ANNUAL REPORT
OF
PROGRAM ACTIVITIES
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH RESOURCES
DIVISION OF RESEARCH SERVICES
Fiscal Year 1981

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

DIVISION OF RESEARCH GRANTS

DIVISION OF RESEARCH RESOURCES

DIVISION OF RESEARCH SERVICES

Fiscal Year 1981

ANNUAL REPORT

DIVISION of RESEARCH GRANTS

FISCAL YEAR 1981

CONTENTS

	Page No.
Highlights	iii
Office of the Director	1
Extramural Associates Program	3
Grants Associates Program	9
Grants Inquiries Office	13
Office of Research Manpower	15
Administrative Branch	17
Referral Branch	19
Research Analysis and Evaluation Branch	21
Scientific Review Branch	23
Statistics and Analysis Branch	29

HIGHLIGHTS

- Over 26,000 competing applications, 17,000 noncompeting applications, and 1,200 interim supplements received, processed, and assigned.
- Over 20,000 applications reviewed by DRG study sections.
- Approximately 22,500 queries processed through the IMPAC system and 1,300 requests for information through the CRISP system.
- Several new study sections chartered and flexible study section concept implemented.
- Scientific Review Branch and Statistics and Analysis Branch reorganized.
- Handbook for Referral Officers initiated and Handbook for Project Control Section completed; Handbook for Grants Assistants extensively revised and updated.
- Annual data or extramural trend publications prepared, including Research Awards Index, Medical and Health Related Sciences Thesaurus, "Brown Book" series, and NIH Extramural Trends: 1970-1980, with accompanying slides.
- All fellowship forms and instructions (PHS 416 series), as well as instructions for applying for a Research Career Development Award, revised.
- Research grant application kit (PHS 398) redesigned from a folder with inserts to one self-contained booklet.
- Two meetings held during February 1981 with the Chairpersons of NIH scientific review groups and key representatives of the NIH administration. The Proceedings from those meetings published.

OFFICE OF THE DIRECTOR

Dr. Carl D. Douglass, Director, discussed the NIH extramural program during a panel discussion at WMAR TV, Baltimore, Maryland, November 14, 1980, and a Proposal Development Workshop at the University of North Carolina, Raleigh, North Carolina, April 15 and 16, 1981. In addition, Dr. Douglass spoke about the NIH extramural program at meetings of the National Kidney Foundation, Washington, D.C., November 23, 1980; the American Academy of Orthopedic Surgeons, Las Vegas, Nevada, February 27, 1981; the Artificial Internal Organs Association, Anaheim, California, May 6, 1981; the American Urological Association, Boston, Massachusetts, May 10, 1981; and the Association of Independent Research Institutes, Palo Alto, California, September 18, 1981.

Dr. Douglass is a member of the NIH Resource Allocation Group; the NIH Senior Executive Service Performance Review Board; the Competitive Research Grants Policy Group, Department of Agriculture; and the Editorial Advisory Committee, American Men and Women of Science.

Dr. S. Stephen Schiaffino, Deputy Director, participated in the NIH Regional Seminar, "Administration of NIH Grant Programs," at the University of Washington, Seattle, Washington, October 23-24, 1980. In addition, he gave seminars on the NIH grants peer review process to the faculty of Loma Linda University, Loma Linda, California, April 20-21, 1981; to the Uniformed Services University of the Health Sciences, Bethesda, Maryland, May 27, 1981; and to the research staff of the Chidren's Hospital National Medical Center, Washington, D.C., September 15, 1981. Dr. Schiaffino also gave a slide presentation on the role of DRG at a Staff Training in Extramural Programs (STEP) seminar in December 1980. On April 1-3, 1981, he was a member of the NIH group that visited the Medical Sciences Campus of the University of Puerto Rico to assess their research potential and make the faculty aware of the research and training support programs available from NIH. In addition, Dr. Schiaffino is a member of the Extramural Program Management Committee, the Coordinating Committee on Minority and Women Research and Training, the Research Resources Coordinating Committee, and the Coordinating Committee on Manpower, and has served on a number of other committees examining various aspects of the NIH extramural programs.

Dr. Samuel M. Schwartz, Associate Director for Scientific Review, gave a slide presentation on the role of DRG at a STEP seminar in May 1981. In addition, Dr. Schwartz served on a number of NIH committees, including the Grants Associate Board (Chairman), the Training Design Team, the NIH Consultant File Working Group, the Review Policy Committee, and a number of other committees related to extramural affairs.

The Division continued to meet the career development needs of the staff by encouraging participation in some form of formal training. As a result, over 250 employees enrolled in job related training courses. The number of those attending classes at the University of the District of Columbia as participants in the Upward Mobility Program rose to 17.

The Division's Equal Employment Opportunity (EEO) program continued its efforts to promote equal employment for all persons--without regard to race, color, religion, sex, national origin, age or mental and/or physical handicap. An EEO Specialist was appointed for DRG on May 31, 1981.

On January 27-28 and April 23-24, 1981, approximately 60 Division managers and supervisors participated in a 2-day course entitled "EEO for Supervisors and Managers." The purpose of the course was to provide managers and supervisors with the knowledge and skills to effectively implement Federal EEO policies and regulations.

On March 23-25 and June 24-26, 1981, members of the Director's Employee Advisory Committee (EAC) attended a 3-day course entitled "EEO for Advisory Committee Members." The course provided members with a clearer understanding of the EAC's roles and functions and effective techniques to accomplish EAC goals.

DRG, with the National Institute of General Medical Sciences (NIGMS), sponsored a 2-day workshop, "Moving Up the Ladder," on April 21-22, 1981. Jan Lynch of McClure Lundberg Associates, Inc. instructed participants on acquiring skills in job-hunting and career changes.

DRG employees participated in "Career Options in the 80's," presented by the Federal Women's Program (FWP) and NIH Women's Advisory Committee (WAC), May 18-22, 1981. A variety of programs and activities were presented on career possibilities and enrichment.

EXTRAMURAL ASSOCIATES PROGRAM

Major Developments

A new Director was appointed to head the Extramural Associates Program in October 1980.

Twelve Extramural Associates from minority institutions will have been in residence and completed the Program during the current fiscal year. (See the attached listing of Associates.) This will bring the total number of resident completions since the Program began in 1978 to 32, with Associates from 21 different states and territories.

Orientation and weekly scheduled seminars for fiscal year 1981 included a series of 104 lectures and conferences covering issues pertinent to the NIH grant and contract processes, Bureau, Institute, or Division intra- and extramural activities, and research programs of other Federal agencies.

Each group of Associates participated in a 5-day Congressional Operations Institute offered by the Government Affairs Institute and made site visits to the National Institute of Environmental Health Sciences and the Environmental Protection Agency at the North Carolina Triangle Park Research Center.

Beginning in fiscal year 1981, Extramural Associates planned, with their respective Advisors, and carried out 10 home institution site visits to encourage increased and expanded utilization of the Associates' newly acquired expertise, and to convey to the institutions the firm commitment of the NIH to aid and encourage increased participation in biomedical research.

Certificates were awarded during this fiscal year to all former Extramural Associates in recognition of the successful completion of the Program, with the award of certificates becoming a permanent practice for all future Associates.

Twelve colleges and universities in North Carolina, Tennessee, Texas, New Mexico, and Michigan were visited by the Program Director to publicize the Program and to discuss with institution presidents, deans and top officials the purpose, requirements, and objectives of the Extramural Associates Program. The approach has proven highly productive; 50 percent of the candidates for the 1981-82 program year have been selected and scheduled to begin their residencies as the direct result of these visits. All 12 vacancies for the 1981-82 program year have been filled.

In addition, scientists and administrators from Florida A&M University, Notre Dame College of Ohio, Elizabeth City State University of North Carolina, and Oakwood College in Alabama have visited the Program Director at NIH seeking further information regarding requirements for admission to the Program for the 1982-83 program year.

National publicity efforts were carried out during fiscal year 1981 through the use of Extramural Associates Program exhibits at the national conferences of the National Association for Equal Opportunity in Higher Education (NAFEO), held in Washington, D.C., and the Minority Biomedical Support Symposium, held in Albuquerque, New Mexico.

Program announcements for the 1982-83 program year have been mailed across the United States to 375 administrators and scientists in colleges and universities that significantly contribute to the pool of minorities and women in science.

Program Effectiveness

During fiscal year 1981, a survey was conducted by the Extramural Associates Office to assess program effectiveness as viewed by former Associates and participating institutions. Associates reported having made useful NIH contacts and having shared acquired Federal grants and contracting information with colleagues at their respective institutions.

Continuing communications between the NIH Extramural Associates and participating institutions will be strengthened with the publication of the first Extramural Associates Bulletin prior to the close of the current fiscal year.

Program Trends

Program objectives include contacting the more than 300 minority and women's colleges and universities across the nation to stimulate all who choose and are able to participate in the resources of the NIH.

Future trends of the Extramural Associates Program will be focused upon:

- stimulating the participation of more minority and women scientists in mainstream biomedical research activity through increased research funding;
- expanding the base of colleges and universities who are able to participate in the Program;
- identifying potential nominees from a broader universe who will lead the future trends at the institutional level; and
- maximizing the participation of minority and women's colleges and universities in federally funded health research.

Site visits are planned to meet with university presidents, deans, science faculty, and administrators so as to broaden the resource base, stimulate participation in biomedical research, develop expanded person-to-person contacts, and fully encourage the nomination of candidates for the coming years.

In order to further these goals, the NIH Deputy Director contacted the National Association for Equal Opportunity in Higher Education during fiscal year 1981, urging its affiliates to nominate candidates for the Extramural Associates Program.

The Program has developed high national visibility and is having significant positive impact upon the image and reputation of the NIH among institutions across the nation that contribute most to the pool of minorities and women in science and research. And the Program intends to sustain and strengthen this trend.

EXTRAMURAL ASSOCIATES

August 17, 1980 - January 31, 1981

Associates

Dr. Virginia Caples
Associate Dean, School of Agriculture
Environmental Science and Home Economics
Alabama A&M University
Normal, Alabama

Dr. Arthur P. Carroll
Chairman, Department of Sciences and Mathematics
College of Santa Fe
Santa Fe, New Mexico

Dr. Isabella N. Finkelstein
Professor of Biology
Clark College
Atlanta, Georgia

Dr. Pauline Komnenich
Assistant Dean for Nursing Research
St. Louis University
School of Nursing
St. Louis, Missouri

Mr. Dennis Strete
Associate Professor of Biology
Tougaloo College
Tougaloo, Mississippi

Dr. Willie J. Washington
Associate Professor of Biology
Central State University
Wilberforce, Ohio

Advisors

Mrs. Barbara S. Bynum
Assistant Chief for Special Review, Scientific Review Branch, DRG
Westwood Building, Room 2A11
496-7558

Dr. James F. Kavanagh
Associate Director for Program Development
Center for Research for Mothers and Children, NICHD
Landow Building, Room 7C03
496-5097

Dr. Jim L. Shields
Associate Director for Review, Division of Extramural Affairs, NHLBI
Westwood Building, Room 557
496-7919

Dr. William I. Gay
Director, Animal Resources Program, DRR
Building 31, Room 5B59
496-5175

Dr. Anthony A. Rene
Chief, Office of Review Activities, NIGMS
Westwood Building, Room 949
496-7585

Dr. Israel A. Goldberg
Chief, Retinal and Choroidal Diseases Branch, Extramural and Collaborative Programs, NEI
Building 31, Room 6A08
496-5983

EXTRAMURAL ASSOCIATES

February 6, 1981 - July 31, 1981

Associates	Advisors
Dr. Leroy Davis Assistant Professor of Biology Department of Natural Sciences South Carolina State College Orangeburg, South Carolina	Dr. Luiz H. Barbosa Program Manager Blood Resources Branch Division of Blood Diseases and Resources, NHLBI Federal Building, Room 5A12B 496-1537
Dr. Vivian G. Howard Professor of Mathematics Department of Mathematics Virginia State University Petersburg, Virginia	Dr. Jane Showacre Executive Secretary, Maternal and Child Health Research Committee Office of Scientific Review, NICHD Landow Building, Room 6C03 496-1696
Dr. Kinney H. Kim Professor and Chairman Physics Department North Carolina Central University Durham, North Carolina	Dr. Luz A. Froehlich Chief, Program and Project Review Branch, Extramural Activities Program, NIAID Westwood Building, Room 704 496-7131
Dr. Annie L. Richardson Professor of Biology Department of Biology Norfolk State University Norfolk, Virginia	Dr. George T. Brooks Associate Director, Extramural Activities Program, NIADDK Westwood Building, Room 637 496-7277
Dr. Charles H. Trottman Professor of Chemistry Department of Chemistry Jackson State University Jackson, Mississippi	Dr. John W. Diggs Deputy Director, Extramural Activities Program, NINCDS Federal Building, Room 1020C 496-4188
Dr. Richie D. W. White Professor of Mathematics Head, Department of Mathematics and Physics Fort Valley State College Fort Valley, Georgia	Dr. Bettie J. Graham Program Director, Retinal-Vascular Disorders Program, Retinal and Choroidal Diseases Program, NEI Building 31, Room 6A51 496-5983

GRANTS ASSOCIATE PROGRAM

Fiscal year 1981 completed the Grants Associates (GA) Program's 19th year. This was a difficult year, because the Program had to cope with two hiring freezes--those of both the previous and the current administrations. Although everyone was affected by these freezes, the GA Program was most affected. Prior to the current administration, four candidates were made GA position offers that were rescinded because of the current administration's retroactive freeze on hiring. The hiring of Grants Associates from within the Department of Health and Human Services is still possible, but that pool has always been a small percentage (10%) of the number of applicants. Throughout the current freeze, Grants Associates can be hired only from that pool; this puts a strain on the system, since Grants Associates, who are essentially pre-health scientist administrators, leave the program at the end of one year.

Because of the impact of the freeze, the Program may be changed. A GA Board Committee evaluated the GA Program's structure, content, philosophy and direction, and submitted its report to the Associate Director for Extramural Research and Training for his review.

This year 11 Grants Associates were on duty - 3 females (27%), 8 males (73%), and 2 minorities (18%). Eight graduated this fiscal year: 6 took positions at NIH (1 each in NIAID, DRR, NIGMS, NIA and 2 at NEI); the 7th took a position in ADAMHA (NIMH), and the 8th is still negotiating for a position at NIH.

With these 8 graduates, the number of GA graduates totals 145: 123 males (85%), 22 females (15%), and 21 minorities (14%). Attachment I indicates where, relative to PHS, GAs took their initial position after graduation. Attachment II shows the man years returned to PHS or NIH relative to the year of training. (These data were part of a larger accumulation of data prepared by Dr. Patricia Straat, GA, for the GA Board.)

The Program's goal of training GAs to assume executive positions has been met, as evidenced by the 1980 Directory of Former Grants Associates, which lists the positions of graduated GAs. Further, the return to the NIH and PHS by the GA graduates is significant. After the GA Program, all but 17 graduates took positions at NIH, and of the remaining 17, 9 took positions elsewhere in the PHS.

Dr. Sara Gardner, Director, Pharmacological Sciences Program, NIGMS, assumed chairpersonship of the GA Board, succeeding Dr. Samuel Schwartz, Associate Director for Scientific Review, DRG.

From the 34 nominations for the Seminar Series this year (32 from NIH and 2 from CDC, NIOSH), 17 nominees, in addition to the Grants Associates and Management Interns, were selected for participation in the Series. One hundred and seventy-six hours of seminar training were offered this year, including six new seminars:

(1) The Impact of Federally Funded Research on State and Local Governments,
(2) The Agency for International Development,
(3) Behavioral Medicine in a Biomedical Research Agency,
(4) Trans-NIH Issues,
(5) Funding Mechanisms, and
(6) The National Toxicology Program.

All Institutes of the NIH were represented in the Series, as were the other PHS agencies, the three National Centers, the Office of Technology Assessment, the Office of Science and Technology Policy, the Office of Management and Budget, the National Academy of Sciences, and the National Science Foundation.

Of the 10 GAs on duty this year, 9 took 12 separate courses. (The 10th GA completed all the coursework in fiscal year 1980.) This totalled 808 hours of training in addition to the seminars, which totalled 180 hours. The average formal training (courses and seminars) per GA was 270 hours--6.75 work weeks, or 13% of the GA year. Hence, on-the-job experience is still the primary mode of training for GAs.

NUMBER OF GRANTS ASSOCIATES GRADUATED PER FISCAL YEAR

Fiscal Year	No. Graduated	First Position
1963	4	4-NIH
1964	8	6-NIH; 1-BSS; 1-left Govt.
1965	14	13-NIH; 1-left Govt.
1966	9	9-NIH
1967	7	5-NIH; 1-BHM; 1-National Center for Urban Indust. Health, PHS
1968	11	8-NIH; 1-BHM; 1-left Govt.; 1 unknown
1969	7	6-NIH; 1-HSHMA
1970	6	3-NIH; 1-left Govt.; 1-NSF; 1-Natl. Center for Health Serv. R&D, PHS
1971	8	8-NIH
1972	7	6-NIH; 1-left Govt.
1973	7	7-NIH
1974	7	7-NIH
1975	5	4-NIH; 1-NSF
1976	9	9-NIH
1977	8	7-NIH; 1-ADAMHA
1978	5	5-NIH
1979	9	8-NIH; 1-ADAMHA
1980	6	6-NIH
1981	8	7-NIH; 1 ADAMHA

Total Number Graduates (as of 7/81) = 145

Average Number Graduated Per Fiscal Year = 7.6

Total Number Enrolled Per Fiscal Year =
Number Graduated in Same Fiscal Year
plus Number Graduated in Subsequent Fiscal Year

Attachment II

GA STATISTICS

Total GAs	140 (Data Unknown for One)
Current Number at NIH	86 (61.4%)
Current Number at PHS	98 (70%)
Number Graduated Five Years or More	108
Spent Five Years or More at NIH	71 (65.7%)
Spent Five Years or More at PHS	86 (79.6%)
Number Graduated Less than Five Years	30
Spent 100% Time at NIH	27 (90%)
Spent 100% Time at PHS	29 (96.7%)
Number Who Spent 100% at NIH	93 (66.9%)
Number Who Spent 100% at PHS	107 (77%)
Number Who Spent 50% (or more) at NIH	103 (74.1%)
Number Who Spent 50% (or more) at PHS	117 (84%)
Number Who Spent 0% at NIH	12 (8.6%)
Number Who Spent 0% at PHS	7 (5%)
Number Who Left NIH After One Year	4 (2.9%)
Number Who Left PHS After One Year	2 (1.4%)
Total Man Years Returned to NIH	896/139
Total Man Years Returned to PHS	1047/139

As of January 1981

GRANTS INQUIRIES OFFICE ACTIVITIES

The Grants Inquiries Office staff replied to more than 10,000 requests for information on the extramural programs, support mechanisms, and the peer review system. Forty congressional inquiries were responded to by letter or telephone, and news releases were prepared on the annual listings of NIH Grants and Awards, the Research Awards Index, and Grants Associates appointments.

Requests for data on NIH-supported research increased during the year. The Office responded to approximately 500 requests that entailed either manual search or computer runs on different research areas or disease entities, grantee institutions, and principal investigators, including NIH support of Nobel Laureates and Lasker Award winners.

Briefings were arranged for visitors from four grantee institutions and business firms during the year. In addition, individuals visiting the Office for information, application kits, and publications continued at about the same level as last year.

The staff updated publications such as DRG Organization and Functions, and submitted to the Office of Information, Office of the Director, revised DRG information for the Scientific Directory and Annual Bibliography, the NIH Almanac, and the NIH Publications List. The National Institutes of Health New Grants and Awards continued to be published quarterly for dissemination to the Congress, the press, and the general public.

Office staff cooperated with the NIH News Branch and DRG staff in preparing an NIH exhibit for the FASEB meeting held on April 12-16 in Atlanta, Georgia. Besides providing informational materials on the extramural programs for the exhibit, the staff also responded to some 300 requests for publications from scientists attending the meeting.

The Office was designated as the distribution point for the following new or revised publications concerning NIH training and special concerns of women and minorities in biomedical research: Research and Research-Related Manpower Development Programs Supported by the NIH (a four-part pamphlet series), Women in Biomedical Research, and NIH Health Research with and for Hispanics.

The Office also made distribution on the new policy brochure and instructions for the Research Career Development Award.

OFFICE OF RESEARCH MANPOWER

The Office of Research Manpower was influential in the revision of several application forms. This included a set of supplemental instructions that enables Research Career Development Award (K04) applicants to use the research grant application form (PHS 398) for competing applications. Those special development awards (K07, K08) using the old application form, PHS 2557-1, will be converting to the PHS 398 form. The program analyst on the office staff also chaired a committee that revised all the forms in the fellowship application series (PHS 416). These forms are now being prepared for submission to the Office of Management and Budget. In addition, the program analyst is serving on a PHS committee, chaired by the Alcohol, Drug Abuse, and Mental Health Administration, which is revising the training grant continuation application. This group is also consolidating the two PHS training grant competing applications (PHS 6025, PHS 2449-1). Separate instructions are being developed for each program. The Office of Research Manpower is developing the instructions for the National Research Service Award. Finally, the Office developed a set of supplemental instructions for the short-term training grant continuation (type 5) application.

In addition to its forms revision activities, Office staff continued to:

- give information and advice to prospective training program applicants and PHS staff;
- provide annual training statistics to the National Academy of Sciences; and
- enhance quality control of fellowship review by monitoring summary statements, conducting meetings of fellowship executive secretaries, and coordinating attendance at BID secondary review meetings.

Finally, the program analyst served on a Fogarty International Center committee, chaired by Mr. James Pike, National Heart, Lung, and Blood Institute, which developed standardized policies and procedures for Fogarty fellowships.

ADMINISTRATIVE BRANCH

The Administrative Branch continued to provide the Division with administrative and financial management (including budget, and scientific evaluation grants), property and supply control, space planning and assignment; to maintain supplies of publications and application forms used in the PHS extramural programs; to be responsible for the efficient running of the components for effective coordination of procedures and services; and to maintain procedures for centralized distribution of application forms by the grantee institutions. A number of studies were conducted or directed by the Branch involving several management activities, which may result in a reorganization or the application of new technology within the Division.

Financial Management Section

The Section assisted in administering about $19 million for the Division's operations, of which $14 million was from the NIH Management Fund, supplemented by $5 million from the Institutes for the support of the Scientific Review and Evaluation Grants (SREGs) awarded to initial review group chairmen. The Section monitored expenditures from these funds through a computer data base system that also provides NIH management with monthly cost analyses progress reports. Consultant costs were again paid almost entirely from the SREGs, with consequent savings in both time and effort. The Section continues to report approximately 9,000 individual payments made to about 3,400 consultants who submitted 7,200 vouchers to the NIH-wide computer-based system for reporting consultants' incomes. In addition to the audit of the 7,200 consultants' vouchers, about 1,200 vouchers were audited by this Section for Division employees and others.

The Section prepared the Preliminary Estimate to HHS, the OMB Submission, and the Zero Base Submission for the fiscal year 1982 President's Budget in addition to furnishing information for the fiscal year 1981 Mid-Year Review. Work has been started on the fiscal year 1983 Forward Plan. The Section continues to monitor the orderly flow of obligations and other aspects of budget execution as well as to respond to requests from the Division of Financial Management.

Office Services Section

The Section continued to review and approve requests for supplies and equipment needed by the Division, to provide property and supply control, and to participate in space planning and assignment. The Section accomplished a number of physical moves, and planned several others, including the accommodation of several new study sections and four new assistant chiefs in the Scientific Review Branch. The Section has also maintained the Division's mail room, and has been responsible for wide distribution of PHS and NIH extramural forms and publications. The Section continued to maintain liaison with other NIH service components for effective coordination of procedures and services, and to be responsible for supplying the control offices of the grantee institutions with application kits.

Previously a folder with various inserts, the research grant application kit (PHS 398) was changed by DRG staff to one self-contained booklet. This reformating not only improved the appearance of the PHS 398, but also facilitated its processing by DRG staff, its distribution to applicants, and its completion by applicants.

The number of grant application kits assembled and handled averaged around 10,000 a month, and about 9,500 miscellaneous packages were mailed each month. The Mail Unit received and processed approximately 35,000 grant applications of all types, as well as a large volume of supporting documents, letters, and publications.

Extensive technical contributions were made by staff in the development of several new and revised forms.

As noted in last year's report, the DRG Reference Room, which had been in operation for 20 years, was disbanded because of space and staff limitations. Reference materials continue to be decentralized into two basic locations, one housing subject reference texts and the other major reference books such as Index Medicus and American Men and Women of Science. A Reference Committee was formed by the Director to ensure the adequate provision of appropriate medical reference materials, and the Section remains extremely active in support of this activity.

REFERRAL BRANCH

At the time this report was prepared, processing for the January 1982 Councils had not been completed. As of July 14, 1981, the Referral Branch had processed and assigned 23,577 competing applications during fiscal year 1981 with an estimated final total of 26,732. In addition, the Branch will have processed 17,413 noncompeting continuation applications by September 30, 1981. The Branch also has processed 1,266 interim supplements as of July 14, 1981.

Staff Activities

During the year, one Assistant Branch Chief and three Referral Officers were appointed.

The Branch Chief participated as a discussion leader in a workshop held by the Training Design Team in April. He also spoke on the functions of the Branch at the Grantsmanship Workshop, sponsored by the National Institute of General Medical Sciences held in May, and participated in the Capital Hill Workshop.

Five employees attended the formal training course entitled "EEO for Supervisors" and one employee attended "The Troubled Employee" course. One employee is participating in the Upward Mobility Program; another employee served on the Employee's Advisory Committee.

Branch Publications

The Branch completed the Handbook for Project Control, which describes the policies and procedures used by the Project Control Section of the Branch for the processing of grant applications. A second publication, the Handbook for Referral Officers, was initiated by the Branch during fiscal year 1981 and will be completed in fiscal year 1982. This handbook contains a description of the policies and procedures used by the Referral Branch for the receipt and assignment of competing grant applications as well as updated referral guidelines for study sections and PHS awarding organizations, and pertinent reference documents.

Processing of Noncompeting Continuation Grant Applications

The processing of noncompeting continuation grant applications (type 5) by the Project Control Section of the Branch has been streamlined. This has significantly reduced the time required by the Branch to process these applications resulting in a more timely receipt of these applications by awarding organizations.

APPLICATIONS PROCESSED BY THE REFERRAL BRANCH IN FISCAL YEAR 1981

Council		May 1981	October 1981	January 1982
Receipt Date		Oct-Nov 1980	Feb-March 1981	Jun-July 1981
			COMPETING	
Number of (1) Applications	New	7704	6425	
	Renewal	2725	1940	
	Supplement	185	153	
	TOTAL	10,614	8,518	4445 (7600)
Distribution (percent)	NIH	79.7	84.3	
	ADAMHA	17.7	12.9	
	Other (2)	2.6	2.8	
			NONCOMPETING	
Type 5		5262	4633	7518[2]
Interim		394	493	379[1]
(Administrative)	TOTAL	5,656	5,126	7,897

[1]Through July 14, 1981
[2]Through September 30, 1980
() Estimated

(1) Includes applications for regular research, program projects, centers, construction, training, fellowships, career awards and minority programs.

(2) Includes FDA, HRA, OH

RESEARCH ANALYSIS AND EVALUATION BRANCH

The Research Analysis and Evaluation Branch assisted several groups with projects that required the use of central NIH data systems. One such project was an investigation of the pattern of scientific review outcomes of a selection of research grant applications involving clinical research. Another was a statistical analysis of the priority scores of research grant applications from study section members before, during, and after service on a study section. In addition, the Branch has taken the lead on a long-term project to determine the feasibility of devising an automated process for identifying and reporting basic research and applied research and development to the National Science Foundation and the Office of Management and Budget. The Branch has been collaborating with the NIH Office of Program Planning and Evaluation and with several Bureaus, Institutes, and Divisions on that project.

The Branch has continued its subject matter analyses in a number of scientific disciplines and special problem areas. At meetings of the Federal Interagency Chemistry Representatives, the Chief represented the NIH and reported on characteristics of the physical sciences chemistry component of NIH-supported research.

A slide presentation depicting several aspects of the participation of research physicians in NIH research grant and training programs was developed for presentation to the Director's Advisory Committee. Similarly the recent trend showing a proportionate decline of participating M.D.s has been documented in a number of ways, including studies of new applicants for research grant support, new principal investigators on R01 grants for the last decade and a half, and all principal investigators on R01 grants.

The Branch has studied the relationship between longevity (as measured by median survival times) of principal investigators in the extramural research grant activities of NIH and their support on NIH-sponsored research training programs. From that study, Branch staff demonstrated that researchers with NIH-sponsored research training support remained active in extramural grant activities for a much longer period of time than those who had no such training.

A computerized file of the fiscal year 1979 NIH Inventory of Clinical Trials has been used to prepare several reports and respond to specific questions in the areas of clinical research and clinical trials. In addition, programming for use of the Grant Applicant File, which has made possible many of our studies on new principal investigators, is being developed to facilitate access to the file by the community of NIH users. An improved standardization of various elements of the File will make it a more reliable base for statistical studies of applicants and awardees and provide links to their prior NIH-sponsored training experiences.

Another revision of the NIH Central Scientific Classification System has been proposed to reduce the amount of work required to classify grants and contracts by field of science to the specifications of annual NSF reports.

Finally, the Branch continues to provide MEDLINE service and assistance to requestors in the Westwood Building and occasionally to NIH health scientist administrators in other rental buildings.

SCIENTIFIC REVIEW BRANCH

The Branch reviewed a record 20,079 competing applications. But the burden was eased somewhat when several new study sections were chartered during fiscal year 1981, including fellowship panels in the Behavioral and Neurosciences, Biomedical Sciences, and Clinical Sciences Review Sections; the Behavioral Medicine Study Section; the Bio-organic and Natural Products Chemistry Study Section; the Physical Biochemistry Study Section; the Experimental Cardiovascular Study Section; and the Experimental Immunology Study Section.

At the same time as these study sections were being chartered, the Branch developed and implemented the concept of the flexible study section. A flexible study section is a chartered study section with provision for a large number of members and a subcommittee structure. The membership can either be (1) subdivided each round into as many subcommittees as needed to review the assigned applications, or (2) subdivided into a fixed number of subcommittees, each operating similar to a regular study section. Thus far, the flexible study sections in the Branch are using the latter process. The Branch currently has seven flexible study sections, four of which review traditional research grant applications and three of which review fellowship applications. These flexible study sections have enabled the Branch to handle the excessive workload efficiently while remaining within the limit of the total number of chartered study sections.

This past fiscal year also saw a major reorganization of the Branch, with the two-fold objective of easing workload and strengthening management. With this reorganization, the four existing review sections (Behavioral and Neurosciences, Biomedical Sciences, Clinical Sciences, and Specials) were enlarged to seven with the creation of the Biological Sciences, Physiological Sciences, and Manpower Review Sections. In addition, the Deputy Chief of the Branch, who previously also supervised a review section, was freed from these responsibilites in order to handle the expanded responsibilities of being Deputy Chief.

With respect to space and equipment, the Branch recently obtained additional space to accomodate the staff increase resulting from the new study sections and reorganization, and has increased its available word processing capabilities. The current equipment in the Word Processing Center will be replaced with 13 versatile IBM Display Writers; it is anticipated that up to 30 IBMs will be in place in fiscal year 1982. This new word processing equipment is designed to improve the quality of summary statements, and also is the initiation of an effort to enable Study Sections to interact with available NIH information resources and services. The Branch's long-range goal is to provide each office with its own IBM Display Writer.

In addition to the above administrative and management developments, the Branch prepared a booklet, entitled NIH Peer Review of Research Grant Applications, to accompany its extensive, ongoing slide collection, and revised and updated the Handbook for Grants Assistants. In addition, Branch staff actively participated in the preparation and distribution of the Orientation Handbook for Members of Scientific Review Groups and the Orientation Handbook for Members of National Advisory Councils and Boards.

The Branch was also actively connected with two meetings in February 1981 involving approximately half the chairpersons of all the NIH scientific review groups and key representatives of the NIH administration. The Office of the

Associate Director for Scientific Review prepared the Proceedings of these meetings, which merged the group discussions and individual presentations into one compact volume. Since the meetings were so well received and productive, the NIH plans to continue such forums in the future.

A major effort during this fiscal year was the development of a merit pay plan specifically applicable to the Scientific Review Branch. In this effort, the Branch Management relied on the recommendations of two committees, one involved with handling the trial run in Fiscal Year 1980, the other with developing evaluation standards and procedures that were consistent with the NIH guidelines yet relevant to the special needs of the Branch. Thus far, the merit pay plan is working well; the performance plans for Executive Secretaries and Executive Secretary-Referral Officers have been favorably received by all concerned, and the progress reviews are on schedule.

Workshops or Symposiums Sponsored by Study Sections

In conjunction with its fall meeting, the Cardiovascular and Pulmonary Study Section held a seminar on the topic of "Animal Models of Aging of the Cardiovascular System." Drs. Myron L. Weisfeldt and Edward G. Lakatta were invited speakers.

Immediately prior to its October 1980 meeting, the Chemical Pathology Study Section completed a two-part workshop on "Chemical Carcinogenesis," which had been initiated in February 1980. Tumor promotion, which was the focus of attention, was addressed by Drs. Emmanuel Farber of the University of Toronto and David Kaufman of the University of North Carolina.

The Microbial Genetics Review Group, in connection with its regularly scheduled meeting, organized a workshop on "Exploitation of Recombinant DNA Techniques" on November 5, 1980. The discussion was chaired by Dr. William F. Raub, Associate Director for Extramural Research and Training, NIH. Also in attendance were Mr. Leroy B. Randall, Chief of the Patent Branch, DHHS, Mr. Richard J. Riseberg, Legal Advisor, NIH, Dr. William J. Gartland, Chief of the Office of Recombinant DNA Activities, National Institute of Allergy and Infectious Diseases, Dr. Ruth L. Kirschstein, Director of the National Institute of General Medical Sciences, and other NIH staff.

On February 25, 1981, the Physiology Study Section planned a workshop entitled "Noise Measurements as a Probe of Ionic Conductance" held at the 25th Annual Meeting of the Biophysical Society in Denver, Colorado. The workshop was organized by Drs. Charles F. Stevens, Robert S. Eisenberg and Martin Frank. This symposium was chaired by Dr. Stevens, had 9 speakers, and was attended by approximately 250 scientists in addition to several members of the Study Section. Its primary purpose was to inform the Study Section members and interested scientists of the correct methodology for the application of noise measurements to excitable and epithelial cell systems. The workshop included a session detailing the history of fluctuation analysis and a description of the correct steps for its application. As a result of the workshop, many scientists, including Study Section members, became aware of a powerful new technique for the study of ionic channels. Plans are currently being made to publish the proceedings as a monograph.

The Reproductive Biology Study Section organized a workshop on "Functional Correlates of Hormone Receptors in Reproduction," which was jointly sponsored by the Division of Research Grants and the National Institute of Child Health and Human Development. The workshop was held at Augusta, Georgia, from October 13-15, 1980, and was attended by about 250 scientists in addition to the Study Section and its Executive Secretary, Dr. Dhindsa. Nine of the workshop speakers were members of the Study Section. The Proceedings of this workshop, edited by V. B. Mahesh, T. G. Muldoon, B. B. Saxena, and W. A. Sadler, were published by Elsevier/North-Holland, Inc. in 1981.

Professional Activities

Besides attending Executive Management Courses, STEP seminars, and other training and development workshops or courses, staff members presented the following papers, lectures, or seminars.

Dr. Edmund S. Copeland, Executive Secretary of the Chemical Pathology Study Section, presented a poster session called "Tips on Getting an NIH Grant" at the Gordon Conference on Oxygen Radicals in Biology and Medicine, on January 12-16, 1981, at Ventura, California.

In December 1980, in conjunction with a personal visit, Dr. Dharam S. Dhindsa, Executive Secretary, Reproductive Biology Study Section, was invited to give seminars on the mission of NIH at the Punjab University, Chandigarh, and the Postgraduate Institute of Medical Education and Research at Chandigarh, Punjab, India. During that time, Dr. Dhindsa also was invited by the Punjab Agricultural University at Ludhiana, Punjab, India, to give a seminar on "The Latest Developments on In Vitro Fertilization and Its Implications." Dr. Dhindsa attended a workshop on "Extra Uterine Fertilization and Implantation," held at Johnson City, Tennessee, on May 25, 1981. At the annual meeting held from August 10-13, 1981, at Corvallis, Oregon, Dr. Dhindsa was invited by the Society of the Study of Reproduction to give a seminar on "How the NIH Grant System Works." Dr. Dhindsa was also requested by the National Science Foundation staff to evaluate the scientific merit of two research proposals.

Dr. Ronald J. Dubois, Executive Secretary, Medicinal Chemistry A Study Section, participated in the Federal Interagency Chemistry Representatives Meeting, held on June 1, 1981, at the National Science Foundation in Washington, D.C.

During the fall of 1980, Dr. Martin Frank, Executive Secretary, Physiology Study Section, was an Associate Professorial Lecturer, Department of Physiology, George Washington University School of Medicine, and lectured in a course entitled "Cell Biophysics." Dr. Frank presented a seminar entitled "Factors Which Influence Reviewers' Decisions" as part of the Biophysical Society Public Science Policy Symposium, "Workshop on Grantsmanship in the 1980's," which was held on February 23, 1981 in Denver, Colorado. He also presented a seminar entitled "NIH Peer Review and Research Funding Mechanisms" to the Department of Physiology and Biophysics, University of California, Irvine, California on April 14, 1981. Dr. Frank presented a seminar entitled "The Peer Review Process at NIH" to the Department of Physiology, Rush University Medical Center, Chicago, Illinois on May 28, 1981. During this fiscal year, Dr. Frank was a member of Research Committee, American Heart Association, Nation's Capital Affiliate.

Dr. Clarice E. Gaylord, Executive Secretary, Pathobiological Chemistry Study Section, was an invited speaker at the November 15, 1980 meeting of the Federal Organization of Professional Women held in Washington, D.C. The subject discussed was career opportunities for women scientists and administrators at the NIH and how research grant applications are reviewed at the NIH. On December 17, 1980, Dr. Gaylord gave a presentation entitled "How NIH Works" to the Washington, D.C. area Network of Minority Women in Science at the Howard University's Student Center. On February 20, 1981, Dr. Gaylord was the guest speaker at a dinner held for the University of District of Columbia's honor biology students. The title of her talk was "Career Opportunities for Biology Science Majors."

Dr. Arthur S. Hoversland, Executive Secretary, Human Embryology and Development Study Section, peer reviewed 5 manuscripts dealing with neonatal lamb mortality submitted to the Journal of Animal Science; peer reviewed 20 manuscripts submitted to a new journal, International Goat and Sheep Research; editorially reviewed 100 pages of Symposia proceedings to be published in the International Goat and Sheep Research Journal; and peer reviewed a BARD research application between the governments of Israel and the United States dealing with the use of a miniature goat as a model in biomedical research. In addition, Dr. Hoversland was invited to prepare a chapter, called "Blood Flow and Oxygen Transport in the Oppossum," in a book entitled The Oppossum as a Model in Biomedical Research.

At the end of September 1980, in conjunction with a personal visit, Dr. Antonia C. Novello, Executive Secretary, General Medicine B Study Section, gave lectures on "Acetate Versus Bicarbonate: State of the Art" at the University of Modena in Italy, and on "Acid Base Balance in Hemodialysis" at the University of Milan in Italy. Dr. Novello was chairperson of a session entitled "Is Bicarbonate Dialysis Really any Better than Acetate Dialysis?" at the Controversies in Nephrology Conference, held at Georgetown University Hospital in January 1981. On January 26, 1981, Dr. Novello gave a seminar on "The Scientific Review Process" at the University of Miami School of Medicine, Bal Harbour, Florida. Dr. Novello was a conference organizer of the Chronic Renal Disease Conference, sponsored by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases held in Bethesda, Maryland in March 1981. Dr. Novello spoke on "Bicarbonate vs Acetate Dialysis," ESRD Network, No. 26, 2nd Annual Nephrology and Transplant Program in Rochester, New York, on April 2, 1981 During the month of September 1981, Dr. Novello was a speaker during a Health Workshop, which is to be part of a Conference sponsored by the Governor's Commission on Hispanic Affairs and the Maryland Commission for Women (September 12); a co-chairperson of the "Extraskeletal Effects of Parathyroid Hormone" session of the 5th International Workshop on Phosphates and other Minerals (September 26); and a speaker at a course in Pediatric Nephrology Update, at the University Childrens Hospital in Bogota, Colombia, South America (September 27).

From January 1981 to the present, Dr. Eileen Raizen, Executive Secretary, Microbial Genetics Review Group has been a member of the Interagency Committee on Microbiology.

Dr. Allen C. Stoolmiller, an Executive Secretary in the Special Review Section, presented a seminar on "The Extramural Grants Program of the NIH" at Northeastern University on October 28, 1980.

Dr. Robert L Straube, Executive Secretary, Radiation Study Section, participated in a symposium entitled "The View from Bethesda" at the Annual meeting of the Radiation Research Society held in Minneapolis, Minnesota on May 31 to June 4, 1981.

Dr. Adolphus Toliver, Executive Secretary, Biochemistry Study Section, spoke on the "NIH Peer Review System and Grantsmanship: A Study Section Perspective" at the Emory University School of Medicine, Atlanta, Georgia, on August 15, 1980; at the Annual Conference of Research Administrators of the California State Universities and Colleges, at Pomona, California, on January 16, 1981; and at the CSUS Research Foundation; California State University at Sacramento, Sacramento, California, on February 19, 1981.

In October 1980, Dr. Constance Weinstein, Executive Secretary, Cardiovascular and Pulmonary Study Section, presented a seminar entitled, "Scientific Merit Review at NIH," at the University of Michigan Medical School. She also participated in a meeting of the Biomedical Research Council of the University of Michigan. Later in the fall, Dr. Weinstein represented the NIH at a "Science Careers Workshop for Women," held in Philadelphia and sponsored by the National Science Foundation. In March 1981, she gave a seminar at the Institutes of Medical Science in San Francisco on "NIH Peer Review of Grant Applications."

A number of DRG staff members, including Drs. Mischa E. Friedman, Richard Peabody, Allen C. Stoolmiller, and Harold Waters, helped operate the NIH Office of Communications' central information booth at the 65th Annual Meeting of the Federation of American Societies for Experimental Biology, in Atlanta, Georgia, on April 12-17, 1981.

Publications

Dhindsa, D.S., Metcalfe, J., and Resko, J.A.: "Oestrogen Concentrations in Systemic Plasma of Pregnant Pygmy Goats." J. Reprod. Fert. 62:99-103, 1981.

Dhindsa, D.S., Metcalfe, J., Blackmore, D.W., and Koler, R.D.: "Postnatal Changes in Oxygen Affinity of Rat Blood." Comp. Biochem. Physiol. 69A:279-283, 1981.

Dhindsa, D.S. and Ochsner, A.J., III: "Hemodynamic Effects of Chronic Carbon Monoxide Exposure in Cynomolgus Monkeys (Macaca fascicularis)." J. of Med. Primat. IN PRESS

Dhindsa, D.S. and Schumacher, G.F.B. (Eds.): Immunological Aspects of Infertility and Fertility Regulation., Developments in Immunology, Vol. 9. Elsvier/North Holland, Inc., New York, 1980. 265 pp.

Klayman, D.L. and Copeland, E.S.: "Radioprotective Agents." Kirk Otheimer Encyclopedia of Chemical Technology, Vol. 19. IN PRESS

Lifshitz, M.L., Wallach, S., and Peabody, R.A.: "Radiochromium Distribution in Thyroid and Parathyroid Deficiency." American Journal of Clinical Nutrition 33: 57-62, 1980.

Marsh, W.R., Rawlings, S.C., and Mumma, J.V.: "Evaluation of Clinical Steroacuity Tests." Ophthalmology 87, 12: 1265-1272, December 1980.

Novello, A.C.: "Pandora's Box Revisited: A Second Look at the Acetate Story" (Invited Editorial). International Journal of Artificial Organs 3(5): Sept. 1980.

Novello, A.C.: "Risks of Cardiovascular Disease in Nephrotic Syndrome." Nephrology Reviews, Vol. II, Diamond, L., and Balow, Jr., (Eds.) Wiley Press, New York, 1981, 86-88.

Ozer, H.L., Slater, M.L., Dermody, J.J., and Mandel, M.: "Replication of Simian Versus 40 in Normal Human Fibroblasts and in Fibroblasts from Xeroderma Pigmentosum." Journal of Virology, August 1981.

Papadopoulou, Z.L., Novello, A.C., Gelfand, M.C., Winchester, J.F., Colon, A.R., and Schreiner, G.E.: "The Use of Charcoal Hemoperfusion in Children." The International Journal of Pediatric Nephrology 1(3): 187-191, 1980.

Peabody, R.A., Wallach, S., Verch, R.L., and Lifschitz, M.: "Effect of LH and FSH on Vanadium Distribution in Hypophysectomized Rats." Proceedings of the Society for Experimental Biology and Medicine 165: 349-353, 1980.

Rawlings, S.C. and Yates, J.T.: "Dynamic Depth-Reversal Stereograms," Annual Yearbook of Ophthalmology, Huges, W.F. (Ed.). IN PRESS

Slater, M.L.: "The Molecular Biology of Budding." Yeast Cell Envelopes: Biochemistry, Biophysics and Ultrastructure, Vol. 11, Arnold, W. (Ed.) CRC Press, Inc., Boca Raton, 1981.

Toliver, A.P.: "NIH Research Grants and Review Process." Proceedings of the Workshop on Proposal Writing for Competitive Grants, Tuskegee Institute, Carter, E. (Ed.), May 1981.

Villarroel, F., Wineman, R.J., and Novello, A.C.: "Past, Present and Future Place of Peritoneal Dialysis." Peritoneal Dialysis Developments in Nephrology, Vol. II, Nolph, K.D. (Ed.) Martinus Nejhoff, The Hague, Boston, London, 1981, 366-383.

Yang, G.C. and Copeland, E.S.: "Spin Immunoassay." Methods in Enzymology, Vol. 74. IN PRESS

Zarate A., Gelfand, M.C., Novello, A.C., Knepshield, J., and Preuss, H.G.: "Propanolol-associated Hypoglycemia in Patients on Maintenance Hemodialysis." International Journal of Artificial Organs 4(3): 130-134, May 1981.

STATISTICS AND ANALYSIS BRANCH

The Statistics and Analysis Branch (SAB) is involved in almost every facet of NIH's extramural activities. Through its IMPAC (Information for Management Planning, Analysis, and Coordination) System, a cental data system on extramural activities, the Branch performs services at virtually every stage of application processing, from initial receipt through award. SAB assists the Referral Branch by providing every two weeks a microfilm containing information on all applications, grant awards, and contracts recorded in the system, and the Scientific Review Branch by providing various documents, such as the Resume of IRG Actions and the application summary statement. In addition, SAB assists the National Advisory Councils and Boards, as well as the awarding units, by providing such services and documents as the Resume of Council Actions and the Notice of Award with the accompanying approval list.

Along with providing these services, the Branch is developing a data base on the extramural activities of the NIH. These data are used to support all levels of NIH management and to provide a source from which NIH can meet its reporting obligations.

SAB also operates CRISP, a sophisticated computer disk storage and retrieval system. CRISP (Computer Retrieval of Information on Scientific Projects) maintains scientific information, under approximately 7,900 subject headings, on all PHS-supported research projects by fiscal year back to fiscal year 1971. CRISP generates annually the 2-volume Research Awards Index that lists the research projects supported by the Public Health Service during a given fiscal year.

Through its two major information systems, IMPAC and CRISP, and other small systems, including the Committee Management System, the Trainee Appointment File, the NRSA Payback File, and the Institution Profile File, SAB provides information services on extramural programs to all levels of NIH management, other Government agencies, and the public at large.

During the past year, the Branch underwent a major reorganization in order to streamline its activities and to provide more effective reporting services to the user community. Under the reorganization, the Office of Systems Planning and the Data Processing Section were merged into a new Systems and Data Management Section. Likewise, the reporting units of the Reports, Analysis, and Presentations Section were reorganized to split the reporting responsibility between NIH users and non-NIH users. The Reports and Retrieval Systems Unit was renamed the Extramural Reports and Information Services to NIH Unit, and the Presentations and Special Projects Unit was renamed the Special Projects and Interface with Non-NIH Systems Unit.

1. Systems and Data Management Section

 The following items were added to the IMPAC System data base during the past year:

 - Ionizing Radiation Code, which identifies research applications that investigate the biologic effects of ionizing radiation;

- Request for Contract (RFC) Date, which is the date an RFC was received by the Bureau, Institute, or Division (BID) Contracting Office;

- Consultant Services Code, which identifies whether the contract is defined as a consultant service contract and the authority for the contract award;

- Prevention Grant/Application Code, which identifies Alcohol, Drug Abuse and Mental Health Administration prevention grants and applications; and

- Percentile Number, which represents the relative position or rank of the priority score among all priority scores assigned during a given initial review and the two preceding reviews.

a. Joint Funding File

A Joint Funding File has been established to accommodate grant awards funded by two or more awarding units. A separate record will be established for each funding BID, which contains, among other things, the dollars awarded by common accounting numbers.

b. Trainee Appointment File

As a result of a survey of principal users of the Trainee Appointment File, 27 data items were dropped from the file. With this reduction in the number of items, the file will be more current. In an attempt to further reduce source data capture requirements, program classification codes in the IMPAC system's Master File Record will automatically be transferred to the corresponding trainee records in the Trainee Appointment File.

c. Computer Retrieval of Information on Scientific Projects (CRISP) System

A QIC (Query via Interactive Communication) program was designed for the CRISP System to provide on-line access to the CRISP database. Records may be selected by investigator name, project and subproject number, or alphabetic term(s).

The CRISP System was redesigned so that duplicate data are not repeated throughout the file. Data that were contained in several records have now been combined in one record, which has resulted in considerable savings in both disk space and also input and output time. In addition, an interactive data capture program has been installed, which makes it possible to increase the number of CRISP file updates. Thus more current and accurate data are being made available to users of the System.

d. Notice of Grant Award

The award statement program was adjusted to print on the new version of the Notice of Grant Award statement, which has four address labels attached directly to the form. This change has resulted in reduced computer and clerical handling time of the awards and labels.

To facilitate quicker turnaround in award statement preparation, the Section is automatically providing the awarding units with grants management and ICMS worksheets two months prior to the next budget period start date. This will give the awarding units more processing time with non-competing grant applications that are received late. In addition, programming changes were made to provide for immediate updating of the Project Address File, which contains the DHHS Entity Number and the grantee and business office addresses that appear on the award statement.

The Section has begun preparation of interactive computer programs to allow for preparation of award statements at the BID level. Once operational, the BIDs will be able to prepare awards daily in their own offices through a CRT terminal and printer.

e. Decentralization of Source Data Capture

Programs and procedures are being developed to automate the application logging system in the Project Control Section, Referral Branch, DRG. Using computer terminals, Project Control staff will log in all grant applications by application number, initial review group, review date, and applicant name. This will establish a preliminary computer record in the IMPAC System and will allow for production of working documents and workload reports on a more timely basis.

f. Personal Data Page

Information from the "Personal Data on Principal Investigator/Program Director" form is now being recorded in the IMPAC System. Birthdate, sex, and racial and/or ethnic origin are being encoded by a special computer encryption routine and stored in the IMPAC file in such a manner that the data can be retrieved only by special decoding techniques. Each application record will be positively coded to indicate whether a Personal Data page was submitted with the application. After entry of the personal data into the IMPAC system, staff shall keep the Personal Data page in a locked file until it has been verified that these data have been accurately recorded in the IMPAC System. Once this verification has been made by IMPAC (normally within one or two days), the Personal Data pages will be destroyed. The personal data items will remain stored in the IMPAC files in special encryption format. Requests for aggregated statistical data regarding these personal data elements will be directed only to the Chief, SAB.

g. ADP Systems Security

An emergency action plan has been developed as required by the DHHS ADP Systems Manual. This plan, which contains procedures for responding to emergencies, specifies the back-up and restoration procedures necessary to minimize the impact of an emergency situation.

h. DSF Lexicon

Programming and processing changes were made to adapt to the new Lexicon of NRSA Disciplines. This lexicon applies to all predoctoral trainees and postdoctoral Ph.D. trainees and fellows under the T32 and F32 grant mechanisms.

i. NRSA Payback

QIC Program. A QIC program was designed for the NRSA Payback File. The program provides on-line access to BID records in the Payback File. Through the use of logic commands, staff in the Office of the Director, NIH, may retrieve records from the file meeting criteria related to the data items.

System Change. In addition to the monthly running of computer prepared Annual National Research Service Payback Activities Certification (APAC) forms, the computer update program has been modified to allow printing of the APAC forms, on demand, for the BIDs. This increased service will save the BIDs time in their follow-up of delinquent APAC forms.

Reports. A series of tabular reports on NRSA trainees and fellows has been developed for the Office of the Director, NIH, for use in program monitoring activities.

New Data Items

- ID of Prior NRSA Grant, which contains the grant number of prior NRSA support, if any, for a fellow or trainee;
- Payback Credit (Regular), which is the number of months of regular payback credit from prior grant(s);
- Payback Credit (Alternate), which is the number of months of alternate payback credit from prior grant(s); and
- APAC Address Control Code, which covers those situations where the APAC form is returned blank or stamped "address unknown."

j. IMPAC System Improvements

The IMPAC Open/Pending History Files were reorganized and updated to improve access and reporting. Grant and contract records are now separated into two main groups, with grant records further arranged by fiscal year.

The code designating foreign applications is now automatically set in the computer based on the FIPS state or country code. This has resulted in a savings of source data capture time in the Section.

k. National Cancer Institute (NCI) Consultant File

Computer programming for a NCI consultant file is now underway in the Section. Biographical and other information on all NCI consultants will be maintained in the system.

l. Study Section Keyword Index

Computer programming for a study section keyword index system was completed this year, and the system is being used for grant application assignment purposes. Cross-referenced listings are prepared either by pertinent study section or by keywords.

2. Research Documentation Section

The Research Documentation Section maintains CRISP, a computerized disk storage and retrieval system, containing scientific data on research grants and contracts supported by the Public Health Service as well as on NIH and National Institute of Mental Health intramural research projects. Through this system, the Section responds to ad hoc and recurring requests for scientific information from Government administrators, scientists, and information personnel to evaluate research programs or specific scientific areas and to prepare reports. Similarly, the Section responds to inquiries from grantee and nongrantee institutions and scientists, the news media, and other non-Government sources concerned with medical research.

Annual publications from the CRISP file include:

- The Research Awards Index, prepared in two volumes. Volume I is a scientific subject index with associated project numbers and titles. Volume II contains project identification data, research contract identification data, and project principal investigator information; and

- The Medical and Health Related Sciences Thesaurus, the vocabulary authority list of subject headings used by the Section indexing staff in indexing research projects.

a. Subproject Information

A significant feature of the CRISP system is its capability of subdividing program project, center, and other large projects into their individual research components thereby providing more detailed and accurate information on the research objectives of these large grants, in addition to the names of principal investigators conducting the research.

b. CRISP Services

During fiscal year 1981, the Section responded directly to over 1,300 requests on a wide range of subjects; prepared videocomp tapes used in the creation of extract Indexes and related material for seven BIDs; provided Scientific Profile data reports and/or CESI tapes for grantee institutions; furnished NIH-wide scientific area data for appropriate BIDs; and performed professional editing operations involving thousands of approved research grant and contract applications. In addition, the Section played a significant role in providing or updating material on various trans-NIH issues.

c. Intramural Research Projects

Professional indexing and entry into CRISP of scientific keyword, title and principal investigator data from fiscal year 1980 intramural research projects were completed soon after receipt of the last annual report in March. This information was subsequently published in the annual NIH-NIMH Intramural Research Index.

d. Research Awards Index (NIH Publication No. 81-200)

Last year, to cut both the cost and size of the Index, its subject section was restricted to include only the primary objectives of each research project. Since this smaller volume was received with overwhelming approval, the current edition published in the spring continues in this abridged format.

e. On-Line Access

Through the CRISP Inquiry System, direct access by the NIH BIDs of the CRISP project narrative, scientific subject, and administrative files has now become routine. To provide a clearer understanding of the content and configuration of the administrative file, a brochure, entitled Descriptions and Specifications of Data Items in CRISP File 3, has been prepared by the Section staff. Recently, a new system "QIC for CRISP" has been developed and introduced whereby, through TSO routines, CRISP files may be iterated on-line in three processing modes: principal investigator name, scientific subject descriptors, and project numbers.

f. Training Course

In January, the Research Documentation Section, in conjunction with the Data Processing Section, presented a description of the CRISP System and provided a "hands on" demonstration of "QIC for CRISP" at the STEP Module on Information Systems at the NIH. This presentation met with an enthusiastic response and demonstrated the need for a more intensive instructional course and laboratory session on the content and use of CRISP. The first such course was given in May, with subsequent sessions to be scheduled.

g. Improvements in Data Processing Activities

Initiatives begun during the last fiscal year for establishment of improved data processing and filing operations have been completed. The new procedures, now fully implemented, have resulted in significant cost savings to the NIH. Currently, steps are underway to update the Section's Vocabulary Unit operations, including reporting procedures on candidate descriptors for incorporation into the Medical and Health Related Sciences Thesaurus.

3. Reports, Analysis, and Presentations Section

The primary function of the Section is to satisfy the information requirements of NIH and PHS centralized extramural activities. In fulfilling this function, the Section utilizes the IMPAC system as well as other data sources. Its responsibilities include design, maintenance, and operation of computer reporting systems; training and technical assistance in data retrieval; planning and coordination of NIH responses to annual surveys covering Federal obligations for research and development (R&D); preparation of formal publications, such as listings of NIH grants and awards and the NIH Basic Data Book; statistical analysis to compile and present visual materials dealing with extramural trends or other topics; and the development and implementation of special evaluation projects. This Section also works closely with the Systems and Data Management Section in maintaining and extending the IMPAC system, and has direct responsibility for establishing institution classifications and related computer files, as well as ensuring the accuracy of selected key data items for publications or reports.

a. Extramural Information Services

Continuing Reports. Approximately 22,500 queries were processed by the Section during fiscal year 1981, primarily in response to requests for information from NIH officials, other Government agencies, and nongovernment organizations. These queries utilized all data capabilities of the NIH IMPAC system, many requiring compiling historical data, designing special reporting files, providing consultation services, and devloping specifications to ensure that requesters' needs were met. The bulk of the queries produced hard-copy listings, but the Section also supplied large numbers of magnetic tapes, which were used by requesters directly to answer questions, or which were entered into other management information systems.

About 175 different reports on currently active or fiscal year awards to date were prepared on regular monthly, quarterly, or annual schedules for extramural program managers and administrators. The data in these reports were organized by geographic location, principal investigator, program class, grant number, budget start date, and other relevant variables. An additional 79 reports were prepared for the

BIDs prior to each round of National Advisory Council or Board meetings, showing detail on competing grant applications. A total of 27 different computer tape transmittals were provided to a majority of BIDs on regular weekly, monthly, and annual schedules. Listings and address labels were furnished to DFM, ADAMHA, HRA, and FDA on a monthly basis, identifying grants for which reports on expenditures were overdue. The Section compiled a number of tables for each quarterly issue of the NIH Management Data Book. Statistical summaries of initial review group actions on competing, research, and training grant applications were prepared during each review cycle, as in previous years.

As of June 1981, 31 institutions were participating in the NIH/Grantee Institution Interface system. This system provides an institution with information on its awards and pending applications in standard had-copy formats, magnetic tapes, or microfiche in exchange for feedback from the institution to NIH concerning the accuracy of the information.

A series of tabulations of R&D contracts were provided to the Division of Contracts and Grants, Office of the Director, quarterly, semi-annually, and annually for inclusion in reports to the DHHS, showing data by BID, type of contractor, type of contract, competitive versus noncompetitive contracts, dollar-award intervals, small businesses, minority-owned and women-owned business organizations, and other variables.

A series of reports on NIH training activities was prepared for the National Academy of Sciences, as in previous years. These reports consisted of 24 tables showing training awards by year, BID, activity, discipline, specialty or field, academic level, and so forth. The Academy was also provided detailed information from each training appointment and fellowship award to update its roster of the individuals supported by NIH training programs.

Publications. The Section devoted considerable effort toward completing three annual Government-wide surveys of research and development. The National Science Foundation survey, entitled "Federal Funds for Research, Development, and Other Scientific Activities," covers all NIH intramural and extramural research activities for the past fiscal year together with the estimated obligations for the next two fiscal years, by performer, field of science, geographic area, basic and applied research and development, and combinations of the above. In connection with its responsibilities for preparing this survey, the Section obtained data from the BIDs allocating the amount of basic and applied research and development for each research grant and R&D contract. The annual survey by DHHS of obligations to institutions of higher education and other nonprofit organizations (known also as the CASE report) required summaries of all NIH extramural support, by activity, for individual institutions and health professional schools. The Section also prepared the NIH response to NIH's own annual survey of obligations for medical and health-related research covering intramural and extramural R&D obligations, by field of science, performer, program, and state.

The Section published the annual "Brown Book" series of NIH extramural awards for fiscal year 1980, including separate volumes on research grants; training, construction, cancer control, and medical library grants; and R&D contracts. The Section cooperated with the staff of the Office of the Director, NIH, in compiling data on extramural activities for the annual publication entitled Basic Data Relating to the National Institutes of Health. An analytically oriented chart book, entitled NIH Extramural Trends, Fiscal Years 1970-1980, was prepared for internal use, along with a set of 35 mm slides to enable these charts and related materials to be presented to various audiences. Additional formal publications of the Section included NIH Fellowship Awards, Fiscal Year 1980 and the quarterly compilation of NIH new grants and awards. Finally, data were provided to the Fogarty International Center for the Statistical Reference Book of International Activities and the companion volume listing each international award.

Initial Review Group Action. Beginning with the May 1980 Council review cycle, a new series of recurring reports was developed to provide additional information on competing applications reviewed and recommended for approval, together with various statistical measures of priority score distributions, such as means, medians, standard deviations, and lowest and highest scores for each study section. These reports were designed to provide information enabling BIDs to evaluate and use actual priority scores for decisions formerly based on normalized priorty scores, which after fiscal year 1980 are no longer available in the IMPAC system. The Section also served as the authoritative source for information on the workload of DRG study sections. Several weeks after the cutoff dates for receipt of applications for review cycles, statistical tabulations were prepared showing the volume of applications to be reviewed by each study section and BID, the type of grant or activity, and, for primary and secondary BIDs, amended applications and dollar values of applications requested. Following the completion of each review cycle, special summaries of DRG study section actions were provided to assist in managing and monitoring their new activities.

Special Projects. During the year, the Section participated in a number of continuing and special projects and studies to develop actual data and projections required for fiscal year 1981, 1982 and 1983 NIH budgets. These included a variety of reports prepared for the Division of Financial Management covering estimated amounts needed to fund research project applications with priority scores of 250 or better, the volume of research project applications reviewed, awards and award rates, and distribution of awards by type of institution, average awards per principal investigator, and so forth. Reports were also prepared showing estimated NIH commitments for fiscal years 1981 through 1986 in order to aid in determining future budget requirements and to ensure consistency and standard presentations of BID projections. The Section participated in the development, testing, and evaluation of alternative solutions for obtaining estimated fiscal years 1981, 1982 and 1983 new research project applications reviewed and recommended for approval in response to the request of the Associate Director for Extramural Research and

Training and the Division of Financial Management. Many different statistical techniques were tested for each BID, such as 3, 5, and 11 year least square line regressions, rolling averages, and parabolic and Gompertz curves. Using a variety of estimating techniques, data were also projected for each BID's renewal and supplemental applications for fiscal years 1981 through 1983.

In order to deal with the problems faced by the BIDs that have relied on normalized priority scores, the Section undertook two major projects. First, in cooperation with the National Heart, Lung, and Blood Institute, a system was developed for ranking grant applications on a comparable basis, using percentile distributions of actual (raw) priority scores. Second, efforts were initiated to acquire a capability to present information on study section behavior using advanced techniques of computer graphics. Beginning with the October 1980 review cycle, a variety of computer-generated charts were developed and distributed to the BIDs and DRG administrative staff to facilitate comparisons of priority scores and recommendation rates for the various study sections.

The acquisition of a computer color graphics terminal and a black and white hard copier has enabled DRG to show data graphically instead of just in a printout. Production is currently averaging about 200 charts per month, which includes sets describing study section behavior, DRG workload trends, and materials to accompany budget projections. The Section is currently preparing a systematic analysis of available hardware, i.e., copiers, plotters, printers, slidemakers, and terminals for future acquisition in providing these services. Assistance and demonstrations have been given to new and potential users of graphics, either individually at the Step Module or at the ADP user's group.

The Section worked closely with staff in the Office of the Director, NIH, in devloping and preparing a set of BID reports on NRSA fellowships and indirect trainees. These reports present the data along two axes: one, scientific discipline, is a group of new lexicon DSF codes; the other, program area, is a grouping of codes unique to each of the BIDs. The Section also developed a lookup table and editing specifications to be used in editing DSF codes in the IMPAC system.

In response to a large increase in requests for reports that compare and/or rank institutions in terms of such factors as dollars awarded, success rates and priority scores, the Section has developed programing and reporting techniques to handle these requests more quickly and in a consistent manner.

The Section continued to play a significant role in the budget formulation process for fiscal years 1982 and 1983. During the past year, computer models were developed to project future competing research project grant requirements; this involved testing and evaluating alternative solutions and techniques and reporting results to the members of the NIH Task Force. The validity of the techniques was discussed with Division of Computer Research and Technology officials. The model presently adopted is based on least square regressions of five years of historical data for each BID. Results

were provided to the BIDs through the Office of the Director for their review and adjustment, based on knowledge of future program changes. In addition, the Section revised the budget data for award rates and unfunded research project applications back to fiscal year 1970 because of the NIH policy change on reporting of carry-over applications. Many new computer programs were also developed for NRSA activities to provide information for future budget submissions. The Section continued to provide payline data for competing research projects, monthly reports on current fiscal year extramural obligations and commitments for all NIH grants, indirect costs as a proportion of total research project costs by institution, and distributions of extramural awards by type of institution.

Many reports on unobligated balances were prepared throughout the course of the year for the NIH Office of Extramural Research and Training to assist the NIH Task Force in determining the effect on NIH extramural activities if a policy change were to be made.

The Section continued to explore ways to more effectively communicate institution-oriented data. It prepared a study of academic departments by grouping the more than 4,000 separate department names into some 50 department groups to facilitate analytical studies. The departments were then consolidated into basic and clinical sciences in order to study the similarities or disparities in their growth patterns over the past six years. In addition, the Section undertook a compilation of data on awards to Black institutions of higher education as well as to institutions of higher education with significant proportions of ethnic minorities.

The Section developed a special presentation on trends in Howard University's awards and competing applications. The materials were used in several NIH briefings and were also made available to the University.

b. Systems Support and Development Activities

Institution Profile File. The Section has established and maintained the Institution Profile File (IPF) to serve as the central registry of names, locations, geographic and other selected data for organizations participating in PHS extramural programs. This file assures uniform reporting and eliminates the necessity for storing similar information in individual grant and award files. In fiscal year 1981, approximately 572 new institution records were added to the IPF, along with more than 25,000 item updates. Also, the addition to the file of the place codes mandated by the Federal Information Processing Standards required 41,000 updates. The IPF now contains about 26,600 records on institutions that have participated in NIH or other PHS activities since fiscal year 1938.

During fiscal year 1981, the Section continued to support the PHS Grants Data System by supplying monthly magnetic tape extracts of all records contained in the IMPAC system for grant awards, and by supplying IPF codes for institutions newly recorded in the Grants Data System. This support ensures consistent and accurate PHS-wide reporting on institutions.

The Section continued to develop and maintain an index of major components and departments for institutions of higher education. A computer program was prepared that ensures consistent coding of applications and awards in order to identify support to medical schools, surgery departments, etc. When this program was first run against fiscal 1980 data, i.e., linking the index against the open file, more than 2,000 cases of erroneous or inconsistent coding were discovered. The application of this program to the open file during fiscal year 1981 on a quarterly basis has uncovered some 200 errors quarterly, reflecting a drastic reduction in the number of inconsistent codes. During fiscal year 1981, approximately 150 new department codes were added to the index, along with more than 7,500 item updates. The index now contains about 21,300 lines, consisting of about 2,200 institutions of higher education, approximately 16,400 major components and departments, and about 2,700 reference lines for internal use.

As in previous years, this Section was responsible for creating and maintaining a special set of fiscal year 1980 "Publication" files, which serve as authoritative sources of data to determine trends, or year-to-year changes, in the amounts and distribution of NIH extramural awards.

Manpower Studies. The Section also continued to operate the system of fiscal year reporting files containing data on professional and other positions paid under NIH research grants and contracts. These data are based on manpower reports that were submitted by principal investigators for awards made from fiscal year 1973 through 1978. The Section responded to numerous requests for fiscal year 1978 updates of previously published tables. In addition, data were furnished by special request for a variety of manpower-related topics. Some of these included detailed data for specific FDS categories, trends in professional-academic doctorate ratios, employment trends within age groups, and requests by program activity as well as divisions with the BIDs.

Report of Expenditures. The Section continued work on the Research Grant Expenditure Report system. This computer-based system currently covers NIH research grants for fiscal years 1971 through 1975. During fiscal year 1981, a contract was awarded and work has recently begun to enlarge this database to cover fiscal years 1976 through 1978.

Budget categories in the IMPAC system refer to the way a grantee expects to spend awarded funds. The Report of Research Grant Expenditure (HEW-489) provides the only detailed accounting of how these funds are actually spent. Expenditure categories that can be compared to budgeted data include personnel, consultants, patient care, travel, equipment, supplies, and alterations. A complex Report Generator program is capable of producing over 3,000 different cross tabulations of these expenditure data, including percent distributions and averages as well as dollar expenditures, each related to numerous grant characteristics.

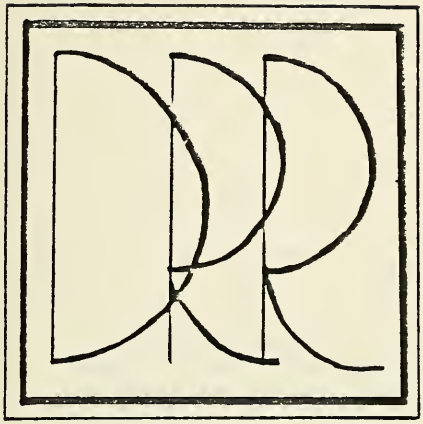
Miscellaneous. Computer programing was started on an NIH reference book summarizing a variety of key data items in the IMPAC system for a five- or ten-year period, such as average lengths of project periods or amounts budgeted by category and BID. In its efforts to keep abreast of rapidly emerging technological changes, the Section continued to investigate other available computer hardware and software.

Retrieval Training. The Section has long been responsible for assisting BID staff in developing and applying systems and programing techniques which would facilitate independent use of the IMPAC system. A senior computer specialist is available and responsible for providing these services on a full-time basis. During the year, two basic courses on how to use the Inquiry and Reporting System were offered, and 45 persons attended these courses. In addition, there was an average of six daily personal consultations.

A short course was held on the software package called the Statistical Analysis System. In addition to discussing fundamental techniques, the course presented some recent applications of the language. Several programs were given out and discussed, so that the attendees left the course with examples that they could use in writing their own programs.

c. Graphic Arts

The Visual Information Specialist finished approximately 1,556 pieces of graphic artwork and photographs. This included charts, tables, certificates, signs, flyers, cartoons, drawings for viewgraphs, viewgraphs, and cover designs for publications and presentations. While most of the work was for DRG, other recipients included staff of the Office of the Director, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, the National Institute of General Medical Sciences, and the National Heart, Lung, and Blood Institute. He designed covers and charts for the following publications: NIH Peer Review of Research Grant Applications, Handbook for Grant Assistants, Handbook for Project Control, Handbook for Executive Secretaries, and Handbook for Referral Officers. In addition, the Visual Information Specialist coordinated work of a contractor (Creative Technologies, Inc.) as follows: 313 new slides, 1,186 duplicate slides, 189 revised slides, and 2,015 color xerox copies. For each slide, the Visual Information Specialist had to have a drawing of what was needed and how it was to be presented; in most cases, he had to create the chart from data supplied. Duties also included advising or consulting with officials concerning the format, color, and composition of slides. He worked on such presentations as Accomplishments, Problems, and Future Plans of DRG, Principal Investigators in NIH Research Grant Activities and Median Survival Times of Cohorts of all new Principal Investigators in Relation to NIH-Sponsored Postdoctoral Training. These studies were to be incorporated in The Forward Plan, given by the Director, DRG, to the Director, NIH. Many of the slides developed for these presentations are used outside NIH by other agencies and universities.



DIVISION OF RESEARCH RESOURCES

ANNUAL REPORT

FISCAL YEAR 1981

(October 1, 1980 - September 30, 1981)

National Institutes of Health
Bethesda, Md. 20205

MISSION:

Identifies and meets the research resource needs and opportunities of the NIH by conceiving, creating, developing, and assuring the availability of those resources that are essential for the efficient and effective conduct of human health research.

Helps institutions establish and operate general clinical research centers where research studies can be conducted on patients over a wide range of human diseases; supports highly sophisticated biotechnology resources, such as computer centers, high voltage electron microscopy centers, and biological structure determination centers; supports primate research centers; increases and improves laboratory animal facilities and resources; makes awards for minority biomedical support, and provides institutional research support for stabilizing and developmental efforts among a variety of institutions throughout the United States.

Provides a unified approach to solving the many complex needs of health-oriented research that tends to be institutional, regional, or national in scale.

TABLE OF CONTENTS

I. Report of the Director..... 1

II. Program Reports

Animal Resources Program.....13
Biotechnology Resources Program.....31
General Clinical Research Centers Program.....41
Biomedical Research Support Program.....59
Minority Biomedical Support Program.....71

III. Office of Grants and Contracts Management.....77

REPORT OF THE DIRECTOR

Dr. James F. O'Donnell
Acting Director
Division of Research Resources

I. Report of the Acting Director

Fiscal Year (FY) 1981 brought significant changes to the Division of Research Resources (DRR) with respect to leadership and organizational goals. Having served most ably for over a decade as the Director, DRR, Dr. Thomas G. Bowery, in December 1980, requested of Dr. Donald S. Fredrickson, Director, NIH, that he be permitted to step down and assume a program role within the DRR. Dr. Fredrickson consented to the reassignment and on January 12, 1981, Dr. Bowery assumed the role of Director, Biomedical Research Support (BRS) Program. Dr. James F. O'Donnell, Deputy Director, was appointed Acting Director of the Division and Dr. Francis J. Kendrick, formerly Director of the BRS Program, became the Assistant Director for Manpower and Resource Development.

In December 1980, the vacancy in the Directorship of the Animal Resources Program, occasioned by the retirement of Dr. Charles McPherson, was filled by Dr. William I. Gay.

At the February 1981 meeting of the National Advisory Research Resources Council Dr. Fredrickson announced that prior to establishing a Search Committee for a new Director of DRR, he wished to examine the broad NIH activities, both DRR Programs and others, which he termed "communal resources," in light of the needs and constraints for the NIH biomedical research effort of the 1980s. He enlisted the Council's assistance, and after meeting with them again at the May 1981 meeting, the Council and DRR top staff developed a preliminary design for a National Research Resources Program. The plan was delivered to Dr. Fredrickson on June 18, 1981, one day before Dr. Fredrickson announced that he was retiring from the position of Director, NIH.

Final design and implementation of the activities encompassed in the plan for a National Research Resources Program have been held in abeyance with Dr. Fredrickson's departure. The Acting Director, NIH, Dr. Thomas E. Malone, has encouraged us to begin assembling data relating to the impact of DRR Programs on NIH activities and the research community. He has also established a Search Committee to select candidates for the position of Director, DRR. The final selection will be made by the new Director, NIH, when that position is filled.

An activity closely relating to our interests in expanding the data base of NIH research resources is the Research Resources Coordinating Committee (RRCC). Moving into its second year of activity, the RRCC began to intensify its exploration of NIH's enterprise of research resources by planning to deal with issues on a longer-range basis, and developing new mechanisms for solving associated problems. Information gathering and exchange were more extensive and covered a broader range of topics. The Committee resorted to various subgroups, advisory committees, and special review committees in order to experiment with and establish new ways to decide about the organizational location, the magnitude of funding, and maintenance of the vitality of different kinds of research resources.

Decisions were made to resolve crisis funding situations and other concerns for such resources as the Laboratory Animal Data Bank of the National Library of Medicine, the Kurland Epidemiology Data Bank supported by the National Institute of General Medical Sciences (NIGMS), and core grants supported by a number of

NIH Institutes. A new technical/conceptual review practice was successfully carried out for the Chemical Information System of the National Heart, Lung, and Blood Institute and the American Type Culture Collection managed by DRR, both of which are funded from the General Expense Fund of NIH. Many other resource program initiatives and issues were dealt with during the year, including the need for animal facilities improvement, the Shared Instrument Grant Programs of DRR and NIGMS, the Regional Medical Library Network, a national data bank for nucleic acids, and the development of an NIH-wide compendium on substances and living materials. The RRCC has taken steps recently to re-examine its role and will be seeking to achieve a number of objectives in the upcoming year. These will include the determination of needs for research resources, the setting of priorities, and the enlargement of its sphere of communication and participation.

In FY 1981, the Division began a comprehensive, systematic effort intended to produce program performance data on all the Division's Programs and major subprograms for use in future program management and planning activities. During March 1981, the managers of all the Division's Programs and major subprograms documented their Programs' objectives and developed indicators of their performance. After clearance and concurrence with the objectives and indicators by the Office of the Director, DRR, and the Office of the Director, NIH, program performance summaries are to be developed for all Programs, using the agreed-upon objectives and indicators as the starting points. Building on the program performance summaries, short-term evaluations will be performed for all the Division's Programs and major subprograms in FY 1982. The program performance summaries developed during FY 1981 will be enlarged during this activity to include FY 1982 results.

The Study, Evaluation of the Role of Clinical Research Centers and Clinical Trials, With Emphasis on Information Processing, (DRR 77-2), was completed in November 1980. The first phase of this Study was completed with the preparation, in December 1979, of an interim report characterizing clinical trials supported by NIH, both within the General Clinical Research Centers (GCRCs) and by the other Institutes. The Study then went on to examine the organizational, administrative, operational, and information-processing needs of the clinical trials carried out on and between the GCRCs to determine whether the Centers are providing an optimal environment for these trials. The final versions of both the interim and final reports were received by the Division in April 1981. The findings and recommendations of the Study are being reviewed by the Program and will be included in future Division planning.

The DRR review function was formally organized into a separate operation with the establishment of the Office of the Assistant Director for Review on July 1, 1980. This organization allows effective coordination of all review-related activities within the Division and has resulted in a greater separation of program and review functions. In FY 1980, primary emphasis was placed on developing standardized procedures and policies applicable to all DRR reviews.

Each of the Division's four committees has review responsibilities. They are the Animal Resources Review Committee which is composed of the Subcommittee on Animal Resources and the Subcommittee on Primate Research Centers; the Biotechnology Resources Review Committee, with its PROPHET Review Subcommittee; the General Clinical Research Centers Committee; and the General Research Support

Review Committee, with its Minority Biomedical Support Subcommittee and Biomedical Research Support Subcommittee. Although Biotechnology Resources grant applications are reviewed by the Division of Research Grants (DRG), the Biotechnology Resources Review Committee evaluates prospectuses submitted for access to the PROPHET Computer System.

During FY 1981, DRR review staff conducted initial reviews of 177 grant applications involving 97 project site visits.

With substantially increasing travel expenses, optional approaches to initial review were explored that did not include project site visits. One was the telephone conference call. A formal committee meeting was held using this process and included the review of seven grant applications. All discussions and voting were done over the telephone with priority scores and votes recorded on voting sheets and mailed to review staff, along with individual review reports after the meeting.

Another process used involved separating each of the individual research projects from their parent grant applications and assembling them according to various scientific areas. Individual panels were convened that consisted of individuals with the appropriate expertise for each scientific area and the projects were assigned to panels accordingly for scientific and technical merit review, a process similar to that conducted by a DRG Study Section. The applications were then reassembled and reviewed by the Program review committee.

Both mechanisms are considered to be suitable for the review of certain types of grant applications and should be useful options in the future.

Applications to the Biotechnology Resources Program continue to be reviewed by DRG. During this past year, close liaison was maintained with DRG. The previous practice of using the project site visit committee as the initial review committee for each application was discontinued. All site visits are now conducted separately with the findings and recommendations documented in individual reports and then forwarded to a Special Review Group, whose membership is represented on each site visit. This Committee completes the initial review by evaluating all applications at one meeting. The result has been higher quality and much more consistency among the reviews, especially in addressing issues unique to the Biotechnology Resources Program.

The Equal Employment Opportunity Committee of DRR planned and held a self-effectiveness workshop for DRR employees. The workshop participants met on four consecutive Wednesdays in the autumn and explored topics including effective and ineffective behavior patterns, sensitivity to the needs and rights of fellow workers, and methods for improving self-effectiveness. The Committee also participated in the "Career Options for the 80's Workshop" which focused on upward mobility and increased awareness of employee opportunities, and the Committee sponsored a series of informational luncheon meetings throughout the year.

In furtherance of the DRR mission, the Office of Administrative Management expanded its support for program planning and analysis by (1) streamlining its procedures for collecting data from the 1980 Annual Reports of Programs. These

data were entered into the DRR information system by student summer employees. The data will be available for analysis and reports in the fall of 1981. (2) Two new subsystems were developed--one is for the data gleaned by the BRS Grant Annual Reports, and the second is a system which will provide very readable information to administrators in the NIH Institutes about their grantees' uses of DRR resources.

A joint project shared by Data Management and Financial Management staffs will result in a computerized system for monitoring the use of full-time equivalent (FTE) hours of employment. This computerized system will provide the needed position management control in FY 1982 and will complement the system currently under development by the NIH.

Major efforts were undertaken to implement the Employee Performance Management System, a methodology for planning and appraising the performance of DRR employees. Similarly, the second year of administering the Merit Pay System and the Senior Executive System within DRR continued. DRR's Personnel staff developed a Program which was well received to honor secretaries during National Secretaries Week, and at which the first annual award to an outstanding DRR secretary was presented. The same staff provided career counseling, not only to DRR employees, but to students and faculty members attending the annual Minority Biomedical Support Symposium.

Other major activities within the Office of the Director centered in the Office of Science and Health Reports (OSHR).

In 1976, OSHR established the Research Resources Information Center (RRIC) to promote the awareness of, the value of, the utilization of, and the access to DRR-supported research resources. Since that time, the Information Officer has offered technical guidance to the Center in order to help it expand its services.

During the fiscal year, the RRIC continued to extend its publications coverage. The circulation of the Reporter rose from 17,000 monthly at the beginning of the fiscal year to 22,000 at the end. Individual requests added to the mailing list averaged approximately 300 every month, and newstand distribution climbed from 5,000 copies per month to 7,000. There are 16 Reporter newstands on the NIH campus and at associated NIH office buildings in Bethesda, as well as in GCRCs in San Diego, San Francisco, and Torrance, California.

Although the Reporter is the monthly mainstay of the RRIC, during the year the Center completed the research, writing, and editing of several special reports with OSHR assistance: "CARTOS" (computer-aided reconstruction and tracing of serial sections) is a 16-page booklet with 10 illustrations that detailed the system which can visually reconstruct neural pathways; the second report was the 32-page "DRR 1980 Program Highlights," a compendium of Division information that included 38 photos and 6 figures.

In addition to the two special reports, the Center also produced during the fiscal year:

Minority Biomedical Support Directory (4th edition)
General Clinical Research Center Directory (3rd edition)

Biotechnology Resources Directory (4th edition)
Animal Resources Directory (4th edition--in press)

All resource directories were extensively revised based on the latest information from grantees as compiled through questionnaires and personal telephone contact.

The Division's publications, produced through the RRIC, continued to be recognized by awards from national organizations:

The "Seeds of Artificial Intelligence: SUMEX-AIM" was awarded first prize for brochures in national competition sponsored by the Health Sciences Communications Association (HeSCA).

The award, presented at the HeSCA annual meeting in May in Philadelphia, is the third for the publication. Previously, the booklet won first prize among technical publications in the National Association of Government Communicators 1980 competition and special recognition in the 1980 annual competition of the American Medical Writers Association, D.C. Chapter.

Earlier in the fiscal year, the American Academy of Pediatrics (AAP) gave its 1980 first-place award for magazine articles to "Anorexia Nervosa Studied at Several Centers," which appeared in the May 1980 issue of the Research Resources Reporter. The award cited the article for "distinguished achievement in pediatric journalism." The prize-winning piece covered research in GCRCs on the contributing and causative factors of the illness, which seems to affect primarily middle-class females.

In addition to the HeSCA and AAP awards, there was recognition for the booklet "1979 Program Highlights--Division of Research Resources." It received honorable mention in the "Other Serials" category at the 19th annual Blue Pencil Awards Program sponsored by the National Association of Government Communicators in Washington.

Through Columbia University, the site of the Biotechnology Resources grant involved, the Center produced a 15-minute film on the CARTOS neuron-tracing system. Information about the film was circulated to medical school faculty throughout the nation, together with copies of the CARTOS booklet. The second phase of the promotion was targeted to officers of neurological and related societies and associations. It asked that they publish an announcement of the film's availability from the RRIC in their publications.

Numerous Reporter articles were reprinted in other publications during the year, through the placement efforts of OSHR. Among the "recycled" pieces, placed by OSHR, after being slightly reworked, were:

Medical Tribune (January 14, 1981) Diaphragm Pacemaker
NIH News and Features (January 1981) Women's Hot Flashes
Medical Tribune (February 11, 1981) Plasmapheresis
Spectrum--CF Foundation (February 1981) Hypogammaglobulinemia
Children Today (January-February 1981) Infant Milk Allergy
NIH Search for Health (March 1981) Cooked Beef Flavor
JAMA (March 6, 1981) Fatal Genetics Disease Therapy

NIH News and Features (March 1981) Alcohol and Sex
Medical Tribune (March 11, 1981) Human Growth Hormone (Part 1)
Medical Tribune (March 18, 1981) Human Growth Hormone (Part 2)
Medical Tribune (April 1, 1981) Human Growth Hormone (Part 3)
Therapaeia (April 21, 1981) Shock Trauma
JAMA (May 1, 1981) Sucrose Polyester
Medical Tribune (May 27, 1981) Chronic Pain

A unique opportunity for the Reporter arose at Pennsylvannia State University. A professor of biochemistry wrote that he was revamping the University basic science course for non-science undergraduates. He felt today's student wanted to know what was going on in the biomedical field, but did not want to become involved in "minutia." In order to make a "relevant, interesting, solid, and comprehensible course for the non-science student," he requested copies of each Reporter issue which would serve as the basic text for the course. He promised the Center an evaluation of the revised course and its new "text."

Interest in Reporter reprints continued strong. The human growth hormone story in the December 1980 issue was distributed by the National Pituitary Agency and the Human Growth Foundation. The Professor of Medicine at Emory University and Director of the Hospital's Clinical Research Center, whose research was featured in the article, wrote: "Your article on growth hormone research was excellent . . . Please send us some copies as we would like to use it here for teaching purposes."

The Principal Investigator of the chimpanzee "language" studies and their application to retarded children wrote for 500 copies of the Reporter reprint.

During the year, with the cooperation and encouragement of the Project Officer, the RRIC converted all volume mailings of Center products to presorted, third-class bulk mail. The back cover format of all publications was redesigned to permit direct address labeling. This conversion is expected to save $125,000 a year in mailing costs.

An index for four years of the Reporter, from January 1977 to December 1980, was being completed as the fiscal year drew to a close. This index will be available to Reporter subscribers early in FY 1982.

In addition to its oversight of RRIC activities, the OSHR created, through numerous other activities, more visibility for DRR grant programs during the year.

Just prior to the beginning of the fiscal year, the OSHR planned and held a media briefing in Rochester, New York, on the liquid protein diet. The briefing explained how researchers had shown that protein diets can cause life-threatening heart irregularities. In clinical trials at a GCRC, serious heart arrhythmias were encountered within 10 days of starting the diet.

The briefing, held at the University of Rochester Medical Center, was attended by science and medical writers, together with radio and TV correspondents. During the briefing, a special conference call network was provided by OSHR to medical writers across the nation.

The Associated Press (AP), United Press International (UPI), Gannett Newspapers, New York Daily News, the New York Times, and other media covered the event with extensive stories. Several radio and television networks carried the story, including the CBS Morning News which sent a reporting team to Rochester.

In another Rochester, the Minnesota home of the Mayo Clinic, the OSHR served as a catalyst for a press conference on the Dynamic Spatial Reconstructor (DSR)--the heart of which is a Biotechnology Resources-supported computer center. The DSR, an advanced x-ray device, allows researchers to view the heart, lungs, and circulation in three-dimensional motion. For this project, the Office helped to prepare the media background materials, helped to arrange on-site details, and was responsible for all national media contacts. Among the news media covering the event were the CBS Network News, New York; the Journal of the American Medical Association (JAMA), Chicago; Minneapolis Tribune; Rochester Post Bulletin; the AP; WTCN-TV, KMSP-TV, KSTP-TV, Minneapolis; KAAL-TV, Austin, Minnesota; KTTC-TV, Rochester; and KROC Radio, KAAL Radio, KWEB Radio, Rochester.

Extensive coverage with credits resulted, including in The Washington Post and syndicate; the New York Daily News; JAMA; The Atlanta Constitution; the Jacksonville Journal; Public Health Reports; U.S. Medicine, plus many other print as well as electronic media outlets. Interest in the story continued for months.

The OSHR staffed a press room at the "First Annual Symposium on Computers in Perinatal Medicine," sponsored by the Perinatal Clinical Research Center of Case Western Reserve University, Cleveland. During the meeting, OSHR set up a press briefing involving caesarian birth rate problems. Based on a large-scale study at the Perinatal Clinical Research Center, Cleveland Metropolitan General Hospital, three obstetricians and gynecologists associated with the Center discussed how a certain number of caesarian deliveries might be avoided. The Cleveland Plain Dealer, the Cleveland Press, UPI, WJKW-TV, WKYC-TV, and WGAR Radio in Cleveland covered the event with additional coverage through a conference call set-up. Articles appeared in the New York Times, U.S. Medicine, Science News, OB-GYN News, and many U.S. publications through UPI syndication.

Based on a cover story in the July Research Resources Reporter, the OSHR held a press conference in conjunction with the University of Michigan Medical Center on the development of a drug pump which could be implanted in liver cancer victims. The research featured the work of the Assistant Program Director of the University of Michigan GCRC. Telephone conference call participants in the press briefing included the AP, Washington Bureau; Reuters - Washington; The Washington Post; the New York Daily News; U.S. News and World Report; JAMA; Bioscience; Medical Tribune; Family Health; the Cleveland Press; American Pharmacy; International Medical Tribune; Gannett News Service; Medical World News; Chicago Sun Times; and National Public Radio. Attending the briefing in person were UPI and UPI Photo; Detroit Associated Press; The Windsor Star; the Detroit Free Press; WNEM-TV; WJLB-TV; WXYZ-TV; WDIV-TV; and WWJ Radio in Detroit. Many national stories resulted which led to numerous phone calls to the Michigan GCRC inquiring about the treatment.

The Detroit press briefing was part of a broad communications plan that the University of Michigan GCRC requested from OSHR. The idea behind the plan was

that the Michigan GCRC should increase its visibility and enhance its image among three important target audiences: medical professionals, mainly practicing physicians, throughout the State of Michigan; University of Michigan Medical Center professional and support staff; and the general public throughout the State of Michigan. To reach these three distinct audience groups different approaches and techniques were required. After OSHR negotiated with the Michigan Medical Society, their journal, Michigan Medicine, ran an article by the Program Director about the GCRC. OSHR helped to write the article and did final editing prior to publication. Several other projects between the Michigan Medical Society and the Michigan GCRC are pending as a result of the Office's personal contact with the Society.

In Cincinnati, the Office assisted with a demonstration of CLINFO at the University of Cincinnati Medical Center. The new computerized data management system for clinical investigators' display was attended by half a dozen media reporters. The showing involved a live television relay from the CLINFO Laboratory at the Medical Center's GCRC to a conference room in the Medical Center Administrative Building.

The OSHR originated the idea for a twentieth (20th) anniversary celebration for the GCRC Program. The Office developed a plaque honoring "20 years of exceptional service devoted to the improvement of human health through the NIH-funded General Clinical Research Center." This plaque was presented by the GCRC Branch Chief at celebrations at medical institutions whose clinical research centers were 20-years old.

The Johns Hopkins Center was highlighted at the first event which was part of the renowned Saturday Morning Physicians Rounds. The Johns Hopkins GCRC Program Director presented a description of the Center, followed by several scientific presentations pertaining to current research protocols by scientists who had used the facility. The Saturday Morning Physicians Rounds are a fixture at Johns Hopkins and attracted about 300 health care professionals to the event.

In December, a special Program was held at Washington University Medical Center to mark the 20th anniversary of its GCRC. The highlight of the Program, which drew an overflow audience, was a lecture by the Chairman of the Washington University Department of Medicine and former GCRC Program Director. The event resulted in extensive media coverage in the St. Louis Globe-Democrat and on several local television and radio stations.

In mid-January, another GCRC 20th anniversary event took place at the University of Southern California Medical Center in Los Angeles. A local U.S. Congressman was the main speaker at the luncheon which honored the GCRC. The local Program Director was interviewed on several television and radio shows and the opportunity for several feature stories in the print media was developed by OSHR.

The University of Rochester was the fourth clinical research center to celebrate its anniversary. The editor of The New England Journal of Medicine spoke at the Medical Center event. The Program Director made numerous radio and TV appearances arranged by OSHR, including on WOKR-TV, WHEC-TV, and WROC-TV. The Rochester Democrat and Chronicle and the Rochester Times-Union also featured stories on the event, plus pieces from suburban and Medical Center publications.

In March, Ohio State University marked the 20th anniversary of its Center with a ceremony highlighted by a talk from a local Congressman. The GCRC Branch Chief presented a plaque and gave some remarks. The activity generated favorable exposure throughout the Columbus area.

Another anniversary event was organized late in the spring with the encouragement and help of OSHR. Yale conducted a formal auditorium program and a "birthday party" for former patients at the Children's GCRC. The activity received extensive media coverage throughout Connecticut and within Yale University. All media contacts were either initiated or coordinated by OSHR.

OSHR helped to plan and produce the dedication of the DRR-supported Primate Research Laboratory at the University of South Alabama. The 10,000 square foot Research Laboratory housed a breeding colony of squirrel monkeys. A media "Open House" was conducted by OSHR during the event. The Mobile Press Register ran a full-page story with pictures. The Pensacola News Journal ran a lengthy feature in the "South Alabama" section. For electronic media, OSHR placed the facility's Director on a five-part TV series over "Newswatch" WEAR-TV, Pensacola, and made other placements on WALA-TV and WKRG-TV, plus WABB Radio, Mobile. The Acting Division Director and the Animal Resources Program Chief were interviewed by Mobile electronic media.

An OSHR staffer served on the Planning Committee for the Ninth Annual Minority Biomedical Support Symposium held in Albuquerque in April. For the ninth consecutive year, OSHR managed the press room for the Symposium and handled all media placements on local TV and radio, as well as national publicity and features. The AP and UPI moved three stories over the wires, including a lengthy feature on the MBS Program Director.

The National Newspaper Publishers Association sent out an advance release and a follow-up picture to over 200 subscribers. All materials were provided by OSHR.

The Sheridan Network and the National Black Network carried guests over their national hookups. Albuquerque television, KOB-TV, KGGM-TV, KOAT-TV, and radio--KZIA, KABQ, KOB, KRKE--conducted numerous interviews with students, faculty, and Program participants during the event, all of which were arranged by OSHR.

The OSHR sent out an advance release to each Program Director at MBS schools in the United States. This "hometown" news story was adapted by many schools to tell the local MBS angle, while pointing up the national Symposium.

Early in the fiscal year, an article on the DRR Minority High School Summer Research Apprenticeship Program was written exclusively for the National Newspaper Publishers Association by OSHR. The article, together with photographs, was issued by the Association to over 200 predominately Black-owned newspapers throughout the United States.

In October, the OSHR staff held a conference for the public relations and information staff persons from the seven Regional Primate Research Centers. The meeting, held at the Yerkes Regional Primate Research Center, Atlanta, Georgia, was to acquaint Primate Research Center personnel with the latest in informational techniques and approaches and how these might be applied to the

Centers. In November, the OSHR staff spoke to the Primate Center Directors at the Washington Regional Primate Center, Seattle, in order to acquaint them with the earlier meeting and to improve their awareness of the role of the information person at their Center.

A lengthy two-part article in the Washington Star on "Artificial Intelligence--SUMEX-AIM" in December was initiated by OSHR during the previous summer. A hand-delivered press kit, including a copy of "The Seeds of Artificial Intelligence" and an invitation to the Artificial Intelligence Workshop at Stanford University, was given to the writer. The author accepted OSHR's invitation to attend the Workshop, and interviewed many of the major participants. Upon her return to Washington, she contacted the OSHR office, and arrangements were made for several interviews with the prime NIH contact, a DRR Program official, who was quoted in the lengthy story.

With respect to Division publications, during the first six months of the fiscal year, prior to the onset of the Office of Management and Budget's printing moratorium, the OSHR handled the printing of the following publications: "Do We Care About Research Animals" (reprint); "Division of Research Resources Five-Year Plan"; "General Clinical Research Center Patient Information" (reprint); and "The National Institutes of Health Minority (Extramural) Research and Training Programs" (reprint). All clearance and bulk printing of RRIC publications were also handled through the Office.

In addition, the Office received and processed approximately 55 Freedom of Information requests. Approximately 300 hours of clerical and professional time were spent handling these requests. The Office also handled 114 Privacy Act requests which, for the most part, were for copies of summary statements of grants before the National Advisory Research Resources Council. These requests took approximately 475 hours of clerical and professional time.

Finally, a total of 13,162 publications was distributed through the Office during the year. The Office received 7,553 individual mail requests; 305 individual telephone requests, including Congressional inquiries; and 80 individual walk-in requests.

Animal Resources Program

INTRODUCTION

The overall objective of the Animal Resources Program is to support resource projects that provide, or enable scientists to use effectively, animals in human health related research. Special attention is given to those animal resource activities that are broadly supportive of the missions of the various NIH components. The objectives are accomplished through the Primate Research Center Program and the Laboratory Animal Sciences Program.

PRIMATE RESEARCH CENTERS PROGRAM

The Regional Primate Research Centers Program was initiated by NIH during the period 1961-1965. The original objective was to meet a recognized need for suitable facilities and appropriate research environments where biomedical research employing the nonhuman primate could be best conducted. Seven Regional Primate Research Centers (RPRCs) were constructed, equipped, staffed, and became operational as unique research institutions by 1965. These Centers and their respective locations are: University of Washington RPRC, Seattle, Washington; Oregon RPRC, Beaverton, Oregon; California RPRC, Davis, California; Delta RPRC, Covington, Louisiana; Yerkes RPRC, Atlanta, Georgia; New England RPRC, Southborough, Massachusetts; and Wisconsin RPRC, Madison, Wisconsin. Each Center is affiliated with a host academic institution. The Centers have resources and research environments which are suitable for a broad range of biomedical research. The Animal Resources Program provides core operational support for the Centers through resource grants. Research projects at the Centers are funded largely by NIH categorical Institutes, other Federal agencies, and private foundations through grants and contracts. which are held by core staff and collaborative and/or affiliated scientists. Through their use of nonhuman primate models, these scientists have made numerous important contributions to biomedical research. During the past year, investigations have been carried out in various biomedical areas, including reproductive biology, infectious diseases, behavioral sciences, neurosciences, toxicology, nutritional and metabolic diseases, and environmental health.

Core support in the amount of $17.213 million provided by this Program in fiscal year 1981 enabled the 150 core staff, doctoral-level scientists to conduct research in the Centers. In addition, the resources and services of the Center were made available to 554 affiliated, collaborative, and visiting scientists from various academic institutions. Research training environments were provided for 181 graduate students engaged in thesis related research. The Program provided salary support for 665 doctoral level, technical, and administrative staff personnel.

On a regional basis, the Centers provided a total of 7,700 biological specimens to 351 scientists at various research institutions throughout the United States. Scientific productivity within the seven Centers has remained strong during the past year, with 696 journal articles and books published by the core staff and affiliated/collaborative scientists.

Because of the problems associated with obtaining certain species of nonhuman primates from countries of origin, all seven Centers have continued their domestic breeding efforts. Approximately 2,100 infants and fetuses were produced by the seven Centers in 1980, representing nearly 75 percent of their total primate animal requirements. Nuclear colonies of a number of less commonly used primate species have also been maintaind to assure the survival of these species for potential research needs in the future. A total of approximately 12,000 primate animals representing 45 species were maintained by the Centers in 1980 for research and domestic breeding uses.

Major research emphasis areas and selected examples of research activities at each Center during the past year are as follows:

WASHINGTON REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF WASHINGTON AT SEATTLE

The core research program of the Washington RPRC includes the areas of neurological scientices, cardiovascular function, developmental biology, disease models, endocrinology and metabolism, and craniofacial structure and function. An extensive affiliated scientist program involved over 60 investigators who were engaged in a variety of investigative areas. An example of research activities during the past year is as follows:

Antiplatelet Drugs

During the past year investigators at the Washington Center have continued to screen selected high probability oral agents that modify platelet function in order to determine efficacy and dose regimens. Two to three baboons (Papio cynocephalus) are used continuously in this particular project. The results are of substantial interest in the strategy of designing controlled human clinical trials. In a second set of studies, the effect of cardiopulmonary bypass oxygenation on platelet function was evaluated. The results showed that there is a marked transient defect in platelet plug forming capability during cardiopulmonary bypass that is associated with selected platelet alpha granule release. In a follow-up study, it was shown that the infusion of PGI^2 into the oxygenator at an appropriate dose completely blocked the generation of the platelet dysfunction. These data show that the defect in platelet function is secondary to platelet activation by the oxygenator. Eighteen animals were used in these studies. The publications resulting from this work have created a great deal of interest among clinical circles because they provide insight into an important complication of cardiopulmonary bypass surgery. In a third set of experiments, 10 animals were used to evaluate the thrombogenicity of coagulation factor IX concentrates. These concentrates have been shown to be thrombogenic in hemophilia β patients when given in large volumes, as is required for surgical procedures. By measuring the rate of platelet and fibrinogen destruction, as well as the appearance of platelet alpha granule proteins (PF4 and β-thromboglobulin) and thrombin-derived fibrino-peptides from fibrinogen following the infusion of various commercial factor IX concentrates, it has been possible to provide comparative information on the thrombogenicity of these clinically applied preparations. The use of nonhuman primates in these studies has been of

particular importance and provides unique information of interest to all hematologists caring for patients with hemophilia β.

OREGON REGIONAL PRIMATE RESEARCH CENTER, OREGON HEALTH SCIENCES UNIVERSITY

Major areas of research emphasis at the Oregon RPRC include reproductive biology, perinatal physiology, cardiovascular pathology, cutaneous biology, immunology, nutrition, toxicology, and metabolic diseases and behavior. An example of activities during the past year is as follows:

Cholesterol Gallstones: Plasma Lipoproteins and Bile Composition

Scientists at the Oregon Center have shown that nutritional, endocrine, and genetic factors influence the concentrations and metabolism of plasma lipoproteins. In addition, there are strong indications that these factors affect the development of atherosclerosis and cholesterol gallstones in humans. The latter diseases were demonstrated in squirrel monkeys (Saimiri sciureus), which were fed semipurified diets containing cholesterol and a saturated fat in studies on the relationships between plasma lipoproteins and cholesterol gallstones.

Female Bolivian squirrel monkeys were shown to have a much higher incidence of gallstones and greater concentrations of high-density lipoproteins (HDLs) than male Bolivian squirrel monkeys. Since this is analogus to findings between men and women, Bolivian squirrel monkeys may prove to be a useful model for studies on differences between the incidences of gallstones in men and women.

Comparative studies between both sexes of Brazilian and Bolivian squirrel monkeys revealed that Bolivian squirrel monkeys have more insoluble pigments in the gallbladder bile than Brazilian squirrel monkeys. Concentrations of an unconjugated pigment (bilirubin) are greater in the plasma of Bolivian monkeys than in the plasma of Brazilian monkeys. This increased concentration is associated with reduced rates of clearance from the blood of both bilirubin and sulfobromo-phthalein.

CALIFORNIA PRIMATE RESEARCH CENTER, UNIVERSITY OF CALIFORNIA AT DAVIS

The major reserach areas at the California Center relate to environmental health siences, infectious diseases, perinatal biology, behavioral biology, respiratory physiology, and immunology. An example of activities during 1980 is as follows:

Fetoscopy Techniques for Sampling Fetoplacental Circulation

The goal of this project is to develop procedures which will permit sampling of the fetoplacental circulation in early human pregnancies in order to diagnose inherited genetic diseases, e.g, the fetal hemoglobinopathies. This study has involved the use of pregnant rhesus monkeys and baboons as animal models to advance the technology of fetoscopy and to assess the safety of the procedure for both mother and fetus prior to its use in the human population.

The fetoscopy procedure has been successfully carried out in 19 cases (83 percent of attempted cases) of pregnant baboons between 80 and 100 days gestation. The position of the fetus and the monodiscoid placenta is determined prior to fetoscopy, using noninterventive ultrasonar techniques. The fetoscope is placed directly between the ventral body wall and into the uterus, and an umbilical or placental blood vessel is sampled using a small gauge needle introduced into the fetoscope cannula. After this procedure, pregnant animals are permitted to go to term and compared with a control group to assess any possible perinatal wastage associated with the procedure.

Based primarily on this work with nonhuman primates at the California Center, approval has been granted by DHHS to extend the fetoscopy study to pregnant women who have elected to undergo abortions. The initial application of the procedure in pregnant women is for early detection of inherited anemias; i.e., sickle cell anemia, thalassemia. This progression of events in the development of fetoscopy clearly demonstrates the significance of the nonhuman primate as an animal model in the study of human disorders.

DELTA REGIONAL PRIMATE RESEARCH CENTER, TULANE UNIVERSITY

The Delta RPRC core research programs cover the areas of microbiology and infectious diseases, immunology, parasitology, biochemistry, neurobiology, and urology. The affiliate/collaborative program includes a number of other areas, including vision research. An example of their research projects is as follows:

Leprosy in Mangabeys

A sooty mangabey (Cercocebus atys) which had developed a spontaneous case of lepromatous leprosy was received at the Delta Center early in 1980. Biopsy material taken from this animal was used to inoculate two other mangabeys. Both of these inoculated animals have demonstrated clear evidence of leprosy. The organisms recovered from the index case are indistinguishable from human Mycobacterium leprae.

This primate model of lepromatous leprosy offers exciting potential for further investigations. The model will permit this disease to be studied in a primate host which has never been possible until now. The index case has now progressed to the point where deformities in the appendages have resulted from nerve damage. If this condition can be reproduced in inoculated mangabeys, it will be possible to study new methods of intervention and experimental corrective surgery. The potential significance of a primate model for studies on this disease is underscored by the fact that over 15 million lepers currently exist in the world.

This project represents a cooperative effort between the Delta RPRC and Yerkes RPRC, with four of the animals currently under study provided from the Yerkes Center colony. In addition, efforts on the immunological aspects of leprosy are underway at both Centers, with active plans for further

collaboration in which the Yerkes Center will provide for breeding and reproductive biology studies on sooty mangabeys for this project.

YERKES REGIONAL PRIMATE RESEARCH CENTER, EMORY UNIVERSITY

Research at the Yerkes RPRC includes psychobiology of great apes and monkeys, anatomical and physiology aspects of the central nervous system, muscle pathology, reproductive biology, immunology, and language acquisition. An example of their activities during the past year is as follows:

Long-Term Effects of Radiation Exposure in Rhesus Monkeys

A colony of rhesus monkeys exposed to various types and amounts of radiation has been studied for the past 15 years at the Yerkes Center. The colony includes three types of radiation exposure: 1) atomic bomb detonation at the Nevada test site in 1957; 2) gamma irradiation with cobalt 60 in 1958; and 3) neutron irradiation in 1954. This irreplaceable group of animals has been monitored closely for 25 years and is believed to be the only colony in the world with such a unique radiation exposure history and long-term followup. The colony has shown an extremely high incidence of cancer (48 percent of autopsy cases have had one or more types of cancer), and a majority of these (85 percent) have occurred in radiation-exposed animals. The control animals are comparably aged rhesus monkeys with no radiation exposure. The cancer incidence in exposed animals has increased over time, and even higher incidences of cancer can be anticipated as these animals grow older. The incidence of cancer in which animals have died in various exposure groups includes 58 percent in the atomic bomb exposed group, 75 percent in the neutron radiation exposed group (3 of 4 animals), and 38 percent in the gamma radiation exposed group.

This work will provide important information in regard to the cancer producing potential that may be associated with radiation exposure. Specifically, these studies will provide data relevant to the incidences and types of cancer which occur in a population of aging, radiation-exposed monkeys. The research will also provide information on cancer tissues and cells for a variety of experimental studies as well as data regarding the possible role of cancer viruses in primate tumors. Information will also be available on the long-term cancer producing potential of various types and doses of radiation. These studies should provide data relevant to problems which may occur in exposed human populations.

NEW ENGLAND REGIONAL PRIMATE RESEARCH CENTER, HARVARD UNIVERSITY

The New England Center's core research program covers the areas of microbiology and infectious diseases, psychobiology, comparative pathology, viral oncology, cardiovascular physiology, and nutrition. The Center's extensive affiliate and collaborative research programs include numerous other biomedical areas of investigation. An example of research activities at the Center during the past year is as follows:

Cardiovascular Physiology

The contribution of the renin-angiotensin system and the autonomic nervous system to maintenance of arterial blood pressure was studied in adult Macaca fascicularis (cynomolgus) monkeys. The objective of these studies was to measure the hemodynamic characteristics of reversible renin-dependent hypertension using partial constriction of the abdominal aorta and to study the renal and endocrine responses to infusions of agents into a lateral ventricle of the brain. The renin-angiotensin system influences vascular resistance, sympathetic nervous system activity, renal functin, and blood pressure level. The central nervous system influences autonomic function, the renin-angiotensin system, endocrine functin, and salt and water balance. All of these components of the cardiovascular, endocrine, and nervous systems are involved in experimental models for producing and maintaining arterial hypertension.

After experimentally producing acute renin-dependent hypertension in Macaca fascicularis, studies with this model revealed a dependency on the renin-angiotensin system and the ability to block any rise in arterial blood pressure by injecting converting enzyme inhibitor (teprotide). Several synthetic peptides that are competitive inhibitors of renin were tested in this model to demonstrate the feasibiity of blocking the actions of renin directly.

Acute hypertension in M. fascicularis was also produced by infusions of angiotensin II while measuring renal function, blood pressure, drinking behavior, and endocrine responses. Additional experiments demonstrated the physiological effects of agents administered to animals who became renin-dependent through aortic constriction or following sodium depletion. Future studies will be directed toward determining the contribution of central nervous system function in renin-dependent hypertension.

WISCONSIN REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF WISCONSIN AT MADISON

Focused areas of research at the Wisconsin Center include endocrinology, behavior, neuroscience, reproduction, and pathology of environmental pollutants. An example of research performed during the past year is as follows:

Primary Influence of Central Nervous System on Initiation of Puberty

Although scientists have attempted to determine the mechanism of the onset of puberty ("how does puberty start?") for more than a century, knowledge in this area is still incomplete. Studies with rhesus monkeys (Macaca mulatta) at the Wisconsin Center, however, indicate that maturation of the brain (the hypothalmus) which stimulates the release of luteinizing hormone releasing hormone (LHRH) is a key factor for the initiation of puberty. LHRH is known to stimulate the release of pituitary gonadotropin (LH and FSH) which facilitate the secretion of ovarian steroids (estrogen and progesterone), the maturation of the ovarian follicles, and induce ovulation. Before initiation of puberty, the release of gonadotropins (and LHRH) is very small but is drastically increased during the pubertal period. Furthermore, the increase

of gonadotropins (and LHRH) during puberty is characterized by the release in a pulsatile rhythm (one pulse every hour), and a diurnal rhythm (more prominent during the night than during the day). Since both pulsatile and diurnal rhythms of hormones are observed in neonatally ovariectomized monkeys when they reach the nominal age for puberty, the ovary is not the organ determining the time of onset of puberty. Similarly, since the pituitary can fully respond to LHRH before puberty, it was concluded that the maturation of the brain is a key factor responsible for the onset of puberty and not the maturation of the pituitary. Although the mechanism of the initiation of the rhythmic and increased release of LHRH is not known, these findings will contribute to understanding the mechanism of puberty and also to establishing a new method for clinical treatment of human patients with delayed puberty.

LABORATORY ANIMAL SCIENCES PROGRAM

The Laboratory Animal Sciences Program (LASP) assists institutions in developing and improving animal resources for biomedical research and training through the award of research and resource grants and contracts. Program areas include support for research related to improving health care and determining environmental requirements of animals used in research; animal colonies of unusual and and special value for research; studies directed at finding animal models which are needed for research on human diseases; projects to assist institutions to comply with the legal and policy requirements for care of laboratory animals; laboratories for the diagnosis and control of diseases of laboratory animals; and research training of specialists in the field of laboratory animal medicine. The Program awarded funds totaling $7.715 million in fiscal year 1981, which supported 60 grants and 6 contracts relevant to animal research or resource projects, 9 institutional training programs, and one individual fellowship award.

RESOURCE RELATED RESEARCH

The majority of projects falling into this category involve investigation of the etiology, pathogenesis, and control of laboratory animal disease problems. For example, currently active projects include the diagnosis and control of mammalian encephalitozoonosis, pathogenesis of parvovirus infection in canines, experimentally induced mucoid enteritis in rabbits, and control of respiratory mycoplasmosis in rodents. The mycoplasmosis project has resulted in development of an enzyme linked immunosorbent assay (ELISA) for detection of anti-Mycoplasma pulmonis antibody in mice and rats. Results to date indicate (1) a continued high incidence of mycoplasma infections in both conventional and cesarean derived and barrier maintained colonies, (2) cultural isolation of the organisms in barrier maintained animals appears to be more difficult than conventional animals, which may be due to environmental differences or bacterial synergism, and (3) the absence of infection in isolator maintained animals suggest that ELISA false positives are minimal. Thus, the ELISA test appears to be a sensitive, specific diagnostic test that has many advantages compared to other available diagnostic tests, especially for wide-scale screening.

In addition to disease related studies, several projects involving population studies, classification, and breeding of nonhuman primates are currently

active. The population studies include a long-term evaluation of natural rhesus populations in northern India and definition of important habitat features for West African rain forest primates. Extensive field work in Peru, Brazil and Colombia plus study of museum specimens is currently underway as part of a comprehensive project to establish definitive taxonomies of the various cebid monkeys with particular attention to those species of significance to biomedical research; namely, Saimiri (squirrel monkeys) and Aotus (owl monkeys). Present taxonomic classification of these latter species is confusing and incomplete. Better definition is critical to captive propagation and research efforts which may depend on demonstrated linkages between genotype and phenotype. The eventual goal is to publish the information as Volume 2 of Living New World Monkeys (Volume 1 dealt with Callitrichidae, the family that includes marmosets and tamarins).

A relatively new project (initiated in 1979) involves genetic investigations in rhesus monkeys at the Wisconsin Regional Primate Research Center. In particular, additional genetic markers are being sought in order to develop a multiple locus measure of inbreeding. This work is an extension of previous efforts to identify usable polymorphisms in rhesus monkeys for parentage identification. Information from this project will be important in understanding and measuring inbreeding in captive populations, particularly with the limited importation of new animals to augment existing breeding colonies.

The number of resource related projects has been relatively level in recent years (9-12 active projects). There is a growing recognition that naturally occurring laboratory animal diseases and environmental factors can have a significant effect on research projects. In recognition of this need, the support of research projects dealing with important laboratory animal disease problems was selected for emphasis in the recently prepared Five Year Plan.

ANIMAL MODELS AND SPECIAL COLONIES

The major objectives of this program area are: (1) to define, characterize, and exploit the relevant biological attributes of selected animals which display potential for use in several areas of biomedical research and (2) to establish, improve or expand special colonies of well characterized animals which are of proven value for biomedical research, but which are not generally available from other sources. Projects aimed at the first objective are of two general types.

The first is represented by two active resources (Washington State University and Michigan State University) which involve a multidisciplinary effort to identify, characterize, and make available new animal models of human genetic diseases. Input regarding potential models is sought from a variety of sources, including animal clinics, veterinary practitioners, and breeding associations and clubs. The oldest resource of this type is at Washington State University. This group has worked with 30 animal models or potential animal models during the past three years including 7 new ones recognized during this period. Some are now well established and have separate grant support including Ehler-Danlos syndrome of dogs, mink and cats (autosomal

dominant disease with defective collagen formation), combined immunodeficiency disorders in horses, and juvenile type diabetes mellitus in dogs. Other models are still in the early stages of development such as mucolipidosis in cats, inherited feline tremors, and inherited canine myasthenia gravis. The general approach is to establish colonies of affected animals and begin characterization studies, often in collaboration with experts at other institutions who are interested in a specific model. Animals and materials from the various models are made available to interested investigators. Ultimately, some models may be transferred to other groups with the interest and expertise to carry on further studies.

Other animal model projects are oriented around selected species which have potential utility as models in more than one categorical area of research. Several marine invertebrate projects, in particular, exemplify this approach. Declining natural populations and problems of maintaining species such as the sea hare, Aplysia californica, sea urchins, Strongytocentrotus purpuratus, and loliginid squids have limited research utilization in the past. Development of mariculture and maintenance techniques could favor laboratory breeding over procurement from the ocean and lead to a continuous source of species wherever they were required. Considerable success has been achieved in maintaining adults of these marine species under laboratory conditions. For example, at the Kerckhoff Marine Laboratory, California Institute of Technology, a culture maintenance system for sea urchins has been developed which can contain up to 3,000 adults. This system provided sea urchin eggs and embryos throughout the year for a laboratory group of 20-30 individuals and during "out of season" periods for other workers. It is now possible to stock and reuse animals for several years. Increasing environmental pressure (chemical pollution, commercial collections for food) gives added impetus to current goals of this resource relative to finding new deep-water populations developing cryogenic methods for storage of fertilized eggs and embryos, and growing sea urchin larvae and carrying them through metamorphosis in the laboratory.

Special colony projects combine in varying degrees the maintenance and production of special strains or stocks of animals with ongoing research to further development and characterization of the models. Currently supported projects include a hamster resource at the University of Texas, Dallas; a bullfrog (Rana catesbeiana) resource at Louisiana State University; a congenic mouse resource at Sloan-Kettering Institute; a rabbit inbred and mutant stock resource at the Jackson Laboratory; and a mouse mutant gene resource also at the Jackson Laboratory. The latter project is typical of this group. The original mouse colony included some 140 mutants with a focus on endocrine, neurological, and immunologic problems. The specific aims are to maintain these well-defined stocks to discover new mutations in the mouse and develop stocks of new and established mouse mutations for use as animal models in biomedical research and to make mutants available to the scientific community. Nearly 3,500 mice were supplied to investigators last year either as breeding stock or experimental animals. A charge is made for this service and the funds are returned to the grant. New mutations kept for further study include an autosomal mutation affecting myelin, a recessive autosomal mutation that affects balance and an inherited hypothyroidism. The mutant

gene in the latter model is inherited as an autosomal recessive gene. The thyroid gland in these mice is small and produces almost no T_4 (one of the thyroid hormones). Their symptoms are almost identical to primary hypothyroidism in humans, and future work with this mouse mutation will be aimed at gaining an insight into the cause of human primary hypothyroidism.

Support for projects related to animal model development and the establishment of special animal colonies decreased from the previous year's level; i.e., FY 1980 - $1.912 million (25% of LASP budget) versus FY 1981 - $1.623 million (23% of LASP budget). A total of 15 projects received support, compared with 24 in FY 1980. This reduction was in keeping with the Five Year Plan which provided for decreased emphasis in this area, particularly if funds were reduced for the program. The development and characterization of new models did receive special consideration as evidenced by the one new award in this area, i.e., to develop laboratory culture techniques of Octopus for biomedical research.

INSTITUTIONAL ANIMAL RESOURCE IMPROVEMENTS

Institutional animal resoure improvement projects are awarded to help institutions upgrade their animal facilities and develop centralized programs of animal care in support of their biomedical research programs. A major objective is to enable institutions to comply with the Animal Welfare Act and DHHS policies on the care and treatment of animals. Requests of this type usually include animal cages to meet current regulations, general sanitation equipment such as cage washers, renovations of animal facilities, and addition of trained professional and technical personnel. The projects are supported for one to three years, after which time the applicant institution is expected to take over complete financial responsibility for its basic animal resource.

Institutional improvement projects have been supported since the inception of the Laboratory Animal Sciences Program. Requests of this type peaked in FY 1973 following implementation of the Animal Welfare Act of 1970 (P.L. 91-579) and the DHHS policy on animal welfare. Over the past 10 years, 113 institutions have received improvement grants with awards totaling approximately $15.0 million. The following figures represent the trend during this period:

	FY 74	FY 76	FY 78	FY 80	FY 81
Reviewed	19	19	21	12	16
Approved	12	9	13	8	16
New Awards & Supplements	36*	6	3	4	2
Total Active Projects	46	21	11	6	7
$ Awarded (in $1,000s)	3229	1289	793	783	298
Percentage of Budget	51%	23%	10%	10%	4%

*Includes applications reviewed in FY 73.

The above chart indicates a relative steady rate of new proposals in recent years. The largest number of program inquiries still touch on this area.

The ability to fund new projects of other types and to combat inflationary costs has come largely at the expense of this program area (note steady decrease in number of active projects and $ awarded). It was possible to fund only one new application and one supplement this year.

Data from the National Survey of Laboratory Animal Facilities and Resources (published March 1980; fiscal year 1978 data) revealed the following facts relative to facilities and equipment:

- Approximately 16 percent of all nonprofit biomedical research organizations reported a need for replacement of some animal facility space now in use, 38 percent reported a need for remodeling to protect the integrity of space now in use, and 43 percent reported a current need for additional space.

- Approximately $350 million is required to meet current needs of nonprofit biomedical research organizations for space replacement, remodeling, and additions to their animal facilities. Another $407 million (using FY 1978 estimated construction costs) will be required to meet space needs projected for FY 1988.

- Nonprofit biomedical research organizations reported a current need in their animal facilities of $43 million for equipment renovation, replacement or additions.

The survey indicates in particular a need for biohazard containment space and equipment, which reflects changes in research activities and increased recognition of the need to contain hazardous agents. In order to meet needs of the scale indicated by the survey, legislative authority (new construction and major renovation) and substantial funding over a period of years would be required.

RESOURCE LABORATORIES

The objectives of these laboratories are to provide for improved animal health programs through appropriate surveillance activities and investigation of naturally occurring disease and other laboratory animal problems, to support studies resulting in new information on diseases of laboratory animals and their etiology, to aid in the elucidation of new laboratory animal models of human disease, and to develop resources including tissues, slides, photographs, etc., for research and training. Resource laboratories have been a major program activity for over 10 years. There has been a continuing turnover in the institutions receiving such awards (support has been terminated for 14 laboratories). The total number has remained relatively constant (13-16) in recent years, and approximately 32% of the budget is awarded in this area. Since resources and trained personnel are limited; laboratories have been confined to those settings with at least several million dollars of NIH-supported research involving the use of laboratory animals. Most resource laboratories are institutional in nature; however, in several instances it has been feasible to serve more than one institution in a metropolitan or regional area.

There are 15 programs which are currently being supported. One new laboratory was funded during FY 1981. This laboratory represents a somewhat different emphasis than previous projects, in that it will deal with marine species. Located at the Marine Biological Laboratory at Woods Hole, Massachusetts, the laboratory will operate on a year-round basis to monitor the health of marine animal used in research at Woods Hole. It will be the first major effort to investigate the etiology of infectious and noninfectious diseases of marine fish and shellfish used in biomedical research. Results of the activities proposed should provide much needed information relevant to the culture, health, and maintenance of marine laboratory animals.

Laboratory activities encompass a broad spectrum ranging from surveillance and monitoring to conduct of research on important laboratory animal disease problems. The laboratories have been productive in terms of new information and techniques. A fatal SV 40 (simian virus 40) infection in a young rhesus monkey was recognized by one laboratory. This agent is widespread in monkey populations and was introduced into many people with some of the early polio vaccines. It had never been associated with a rapidly fatal illness in an otherwise healthy animal before. This case was also of significance because it demonstrated the usefulness of the immunoperoxidase technique in finding virus in autopsy tissues. Bacterial pathogens are commonly associated with serious disease outbreaks that interfere with or compromise research.

Avian tuberculosis was diagnosed in a colony of White Carneaux pigeons used in pharmacologic studies at one institution. Intradermal tuberculin testing proved to be unreliable because of the frequent occurrence of false positive and false negative reactions. Birds not being used were culled from the colony. A protocol was developed for effective quarantine of the remaining animals, routine disinfection of equipment and cages, and protection of personnel to reduce the risks of exposure. Using these methods, the organism was successfully contained until critical studies were completed. The colony was subsequently replaced with animals from another source shown to be free of disease by the diagnostic laboratory.

Recognition of a Salmonella typhimurium-associated conjunctivitis in an adult cat during quarantine led to initiation of a Salmonella screening program at one laboratory in the northeast. A Salmonella carrier incidence of slightly over 10% was detected in rural source cats from commercial dealers. A high incidence of antibiotic resistance was noted in treating affected cats. The fact that clinically normal carriers of Salmonella can shed organisms is of importance to biomedical research because the organisms pose a potential health hazard for persons handling these animals and the stress of hospitalization or surgery may induce severe clinical disease.

Several laboratories are particularly interested in the problem of pasteurellosis, a widespread disease of laboratory rabbits. Unfortunately, Pasteurella multocida infections are not readily controlled through antibiotic therapy, and recurrent infections are common. Current studies range from a characterization of virulence determinants and rabbit neutrophil phagocytosis and/or killing to identification of important serotypes to

vaccine studies using avirulent mutant strains. Several separate research grants have been submitted dealing with specific aspects of this complex problem area. Information being generated has been valuable in understanding the multifactorial nature of this bacterial pathogen and should lead to the development of improved means of control for this important disease.

Recognition of potential animal models is an important aspect of working up problems presented to the laboratory. One laboratory recently recognized an abnormal susceptibility to viral and bacterial infections in a colony of Brittany spaniels with an inherited degenerative disease of the central nervous system. Clinical and diagnostic workups of these animals showed that a group of animals in this coloy were totally or partially deficient in complement (C-3), a blood factor essential for resistance to injury of all types. Although research has only begun, this deficiency appears to be inherited as a simple recessive trait. It is a very rare condition and these animals are extremely important for their potential use in the study of disease resistance and the inflammatory response, not only in dogs but in all animal species.

OTHER PRIMATE RESOURCES

In addition to the seven Regional Primate Research Centers, the Animal Resources Program supports several other nonhuman primate resources. These include three contracts and five grants for the domestic breeding of nonhuman primates. In addition, there is a grant for a Primate Supply Information Clearinghouse. These projects are part of the effort to provide a supply of primates for essential biomedical research in the face of export restrictions and embargoes by the countries of origin. During fiscal year 1981, no wild-caught rhesus monkeys were imported for biomedical research. The supply of other wild-caught Old World as well as New World primates continued to decline due to increasing export restrictions. The three contracts are for the production of animals for general distribution to NIH extramural investigators. The overall goal of these projects is to produce 1,200 rhesus monkeys and 150 cynomolgus monkeys per year. As of June 30, 1981, there were 1,622 female rhesus and 142 cynomolgus in the production colonies. There were 997 rhesus and 118 cynomolgus monkeys born this past year. The polio vaccine testing program took the first 235 male rhesus offspring. All females were kept for colony expansion. In addition, ARB supplied 344 rhesus monkeys to NIH grantees from cull, exchange, or recycled animals. The contracts also supplied 160 young females to Lederle Laboratories for expansion of their colony and provided 78 cynomolgus monkeys to investigators.

The grant-supported primate breeding projects are for establishing nuclear production colonies and determining proper husbandry techniques for maintaining these colonies. Colonies under development are baboons, two species of marmosets, squirrel monkeys, and two species of Galago (bushbabies). The latter project represents the one new award in this category during the current fiscal year. In addition to these breeding and development grants, the Caribbean Primate Center at the University of Puerto Rico has a grant supporting an island colony of 900 rhesus monkeys. These monkeys have genealogy records dating back to 1938, making them very useful for social and

behavior studies. The Center is also conducting some pilot studies on tropical diseases and physiology with primates housed on the mainland. The National Institute of Neurological and Communicative Disorders and Stroke maintains a colony of rhesus at the Center for fetal studies.

The Primate Supply Information Clearinghouse is designed to facilitate maximum research utilization of primates already in this country. The Clearinghouse matches requests for primates, primate tissues, and related services with investigators and breeding colonies who have these items available. The Clearinghouse publishes a weekly bulletin and has handled 735 formal requests for primates and 1,161 informal requests during FY 1981. From these, they placed 3,342 living primates and satisfied 64 requests for cadavers, tissues, and other specimens plus 14 cage requests.

TRAINING

Training in laboratory animal medicine is intended to prepare individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through knowledge of laboratory animal biology and understanding of research methods. In addition, the trainees are prepare to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team.

There are eight currently active training programs with a total of 29 funded trainee positions. In addition to the institutional programs, one individual postdoctoral fellowship was active at the end of the fiscal year. Since the average training period is two and one-half years, there are usually 8-10 graduates per year. Currently available figures indicate that 169 trainees and fellows have completed training since the inception of the training grants and fellowships in laboratory animal science and medicine. Fifty-nine (59) of these are employed by medical schools and 64 by other academic, research or governmental organizations. The majority (104) are serving as directors or staff members of a vivarium; 50 are engaged in teaching and research or are obtaining additional training; and 15 are in public health, private practice or are retired. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

For the past six years, the active training programs and diagnostic resources have been encouraged to employ veterinary students during their summer break. Nine programs and 21 students participated this past year. Critiques of the students involved were submitted to the Branch and, in turn, distributed to all the program directors. It appears that this work experience is resulting in greater knowledge and interest in the field of laboratory animal medicine by veterinary students. Several former summer students entered formal postdoctoral programs this year and development of a "pool" of such individuals for future postdoctoral training should result in long-term benefits to the field.

ADMINISTRATIVE ISSUES

During fiscal year 1981 the effect of earlier proposed legislation to redirect monies scheduled for research using animals to research using technology which might be alternatives to laboratory animals took on a new importance. Interested Congressmen and members of the public were able to pursuade NIH of the importance of this issue and of the need to hold a conference. This resulted in the "Conference on Trends in Bioassay Methodology" held February 18-20, 1981, at the Pan American Health Organization Building, Washington, D.C. This conference produced a record of the advances in technology which might be considered as substitutes for laboratory animals in the pre-clinical phase of research and testing. The state of the art was reviewed by scheduled speakers in an objective way, but the 20 humane society/animal welfare groups who were recognized at this conference were able to build a record favorable to the "alternatives" cause and pursuade many of the senior NIH staff members attending that they represented a signficant political movement. It is expected that this will lead to changes in the way animal research protocols are reviewed, with emphasis on the appropriate use of laboratory animals. It is hoped that Congressional hearings on the alternatives issue can be put in their proper perspective and that the interest in providing for the improvement of laboratory animal facilities and care can be stabilized, if not improved, in the future.

The Animal Resources Program continues to survey the use of laboratory animals in NIH research projects and has obtained data from both the CRISP (computer) system and from personal review of summary statements for FY 1980. These summary statements note the use of laboratory animals in the Description section. Summary data for those study sections in which the most pre-clinical work is done indicate that about 65 percent of these projects use animals, the heaviest use, of course, being of laboratory rodents. This data is similar to that obtained on funded research projects in earlier years. Nevertheless, 13 percent of these research projects continue to use dogs and cats, and well over 5 percent of the projects use primates. There is an increase in the use of farm animals, probably replacing dogs and cats; and there is an increase in the use of marine invertebrate species due to the new opportunities for use because of lower costs and ready availability. The Animal Resources Program will continue to track the use of these animals in the future and is currently considering the funding of more projects in support of amphibian and marine species than it has in recent years.

Table I

Primate Research Centers Program Appliations - FY 1981

Type	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.....	-	--	-	--	-	--
Renewal.....	2	5,649,734	2	5,207,467	2	4,240,744
Supplemental.....	1	2,631,813	1	2,631,813	1	2,666,878
Continuation.....	4	11,928,617	4	10,880,297	4	10,305,303 3/
TOTALS	7	20,210,164	7	18,719,577	7	17,212,925 3/

Table II

Laboratory Animal Science Program Applications - FY 1981

Type	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.....	64	7,241,653	53	4,448,865	6	712,730
Renewal.....	20	2,258,287	20	1,862,469	12	1,502,794
Supplemental.....	8	174,166	8	165,666	8	232,690
Continuation.....	34	3,834,653	34	2,944,767	34	4,157,396
TOTALS	126	13,508,759	115	9,421,767	60	6,605,610

Table III

Laboratory Animal Science Programs - FY 1981

Program	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
Resource Research..	31	1,758,105	23	1,113,574	12	716,593
Primate Resource...	9	1,390,886	9	1,079,803	5	1,019,278
Special Colonies and Models.....	25	2,418,938	24	1,838,599	14	1,566,292
Basic Improvement..	22	3,784,264	22	2,275,711	7	298,190
Diagnostic Labs....	21	3,133,360	21	2,285,339	15	2,275,208
Reference.....	6	676,038	6	554,166	4	634,404
Information & Other	8	200,486	6	131,243	3	95,645
Research Career....	1	37,800	1	37,800	-	--
New Investigator...	3	108,882	3	105,532	-	--
TOTALS	126	13,508,759	115	9,421,767	60	6,605,610

1/ Direct Costs Only
2/ Includes Indirect Costs
3/ Includes Reimbursement Funds ($45,660) from NIA

Table IV

Contract Program - FY 1981

Program	Number Supported	Amount Funded
Special Colonies and Models.....	1	57,043
Primate Supply.....	3	319,952
Program Support.....	2	125,000
TOTALS	6	501,995

Table V

National Research Service Award Program - Institutional - FY 1981

Type	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.....	-	--	-	--	-	--
Renewal.....	-	--	-	--	-	--
Supplemental.....	-	--	-	--	-	--
Continuation.....	8	700,224	8	748,347	8	574,935
TOTALS	8	700,224	8	748,347	8	574,935

Table VI

National Research Service Award Program - Individual - FY 1981

Type	Number Received	Number Approved	Number Funded	Amount Funded
New.....	1	1	1	19,040
Renewal.....	-	-	-	--
Supplemental.....	-	-	-	--
Continuation.....	-	-	-	--
TOTALS	1	1	1	19,040

Table VII

Short Term Training Program Applications - FY 1981

Type	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.....	4	90,450	3	68,340	-	--
Renewal.....	-	--	-	--	-	--
Supplemental.....	-	--	-	--	-	--
Continuation.....	1	50,250	1	24,120	1	13,025
TOTALS	5	140,700	4	92,460	1	13,025

1/ Direct Costs Only 2/ Includes Indirect Costs

Fiscal Year 1981 Annual Report
Biotechnology Resources Program
Division of Research Resources

Background and Summary of Past Accomplishments

The Biotechnology Resources Program (BRP) was initiated in 1962 in response to a Congressional interest that NIH establish an activity focused on specialized equipment needed for biomedical research. Since that time, the BRP (formerly called Special Research Resources) has changed and expanded its scope. While the Program in the early years, mainly supported large general purpose computer centers in medical schools, it later moved into an extremely broad and innovative array of biomedically relevant technologies. In addition, the Program now places greater emphasis on regional and national sharing of resources. Major thrusts of the Program today are applications of biomedical engineering, computer science and knowledge systems to biomedical and clinical research programs, and specialized instrumentation for the study of biological structure and function.

Technical capabilities provided by the BRP continue to be essential for progress in many areas of scientific investigation. Without advanced technological resources, biomedical research scientists would be unable to make important structural and chemical measurements or to handle the vast amount of data required to reach valid scientific conclusions.

Over the years, physical and mathematical theories have been developed and subsequently used by engineers in order to provide responsively important research instrumentation necessary for solving problems in biomedical research. That interface between scientists and engineers, so essential for the scientific advancement of biomedical knowledge, is not always obvious nor easily established. Through its operation at this interface, the BRP has been able to develop and make available advanced, highly sophisticated research tools for biomedical science.

BRP has developed and made available to scientists a wide range of computer systems for study of biomedical problems. Among the more recent are computer systems for applying artificial intelligence methods to biomedical problems, computer graphics systems for study of three-dimensional structure of proteins, nucleic acids, interactions of proteins and drugs, and structure of nerve cells and fibers. The development of the first high field 600 Megahertz nuclear magnetic resonance spectrometer for biomedical research was supported by BRP in collaboration with NSF. BRP introduced the first million volt electron microscopes dedicated to biological research in this country and in the world and supports high resolution scanning transmission electron microscopes used in resolving single atoms in cells and tissues. BRP has made the high intensity and tunable wavelength synchrotron radiation available to investigators for studies involving X-ray diffraction, X-ray spectroscopy and time-resolved fluoresence measurements. Access to laser microbeam equipment for subcellular, cellular and tissue level microsurgery is possible for scientists at a Biotechnology Resource.

FY 1981 Accomplishments

Administrative

New Resources - BRP funded two new resources this fiscal year. A high voltage electron microscopy resource was funded at New York State Department of Health in Albany. The grant expands operation of the Albany high voltage electron microscope by providing funds for addition of another shift for use by investigators in the Northeast part of the country. Research will involve three dimensional studies of cancer cell invasion, structure of spindle components during mitosis, cytochemistry and immuno-labeling of thick sections and whole cells, three dimensional reconstruction of cell organelles by tomography, elemental analysis and electron diffraction of wet specimens using an environmental chamber and high resolution dark field study of the structure of membranes. A resource for high sensitivity multinuclei nuclear magnetic resonance spectroscopy and sophisticated data processing was established at Syracuse University, Syracuse, New York. This Resource will develop probes for optimized high sensitivity ^{13}C and other nuclei, implement a new spectral data processing package having unique capabilities for utilization and presentation of raw spectroscopic data, design a hardware/software system to enable users remote to the Resource to have on-line access to the Resource computer and spectrometer and design a data processing center which allows data base searching activity, numerical computation and computer-assisted communication with Resource users.

A new investigator research award was given to Heang Tuy, University of Pennsylvania, to investigate new methods for three-dimensional computer tomography reconstruction from data from a limited range of views and to compare these methods with existing methods on computer simulated and real clinical data.

New Grant Applications

BRP announced the availability of $2 million of new funds for the support of new grants in the May 16, 1980, issue of "NIH Guide for Grants and Contracts," the August 1980 issue of "Federation Proceedings," and the July 1980 issue of the "Research Resources Reporter." Fifteen type one applications and two supplements were submitted for consideration for FY 1981 funding and to date 21 type 1 applications have been received for review at October 1981 and February 1982 Councils. The increase in number of applications received for FY 1982 funding indicates the long lead-time required for writing BRP grant proposals.

Workshops, Conferences and Exhibits

Seven conferences and workshops were sponsored in Fiscal Year 1981. A conference on high voltage electron microscopy (HVEM) in biomedical research was held November 12, 13, 1980, at the University of Pennsylvania, Philadelphia. The conference summarized the important areas where significant advances in the understanding of biological structure and function have been made through use of HVEM, discussed what future developments in HVEM instrumentation would enhance its capabilities, predicted areas of biological research which can be expected to profit from HVEM in the future and evaluated the need for additional HVEM facilities in this country.

A symposium on structure and dynamics in molecular biology was held to celebrate the opening of the Biotechnology Resources Center at the Stanford Synchrotron

Radiation Laboratory October 22, 1980. Speakers at the symposium included Dr. Hans Fravenfelder, University of Illinois, Dr. Steve Harrison, Harvard University and Dr. Michael Koch of the European Molecular Biological Laboratory.

A meeting of Biotechnology Resources Principal Investigators was held May 1, 2, 1981, in Washington, D.C. Topics discussed were fee for service in Biotechnology Resources, BRP annual progress reports, NIH and DHHS patent policies and the research community's concern over support for Biotechnology Resources.

The annual PROPHET Users' Colloquium was held May 14-16, 1981, at Airlie House, Airlie, Virginia. The 125 scientists who attended represented approximately 35 user sites as well as DRR staff including both the BRP and Minority Biomedical Support Programs. Topics discussed included Extended Least Squares Nonlinear Regression, Managing Very Large Data Bases, the Molecular Pharmacology of Digitalis, the Pharmacokinetics and Pharmacodynamics of Cimetidine, Nucleic Acid Sequence Handling Tools in PROPHET, Quantitative Structure Activity Studies, the use of PROPHET in a Major Clinical Center, the Use of Microcomputers with PROPHET, and PROPHET and Distributed Systems. A series of eight workshops was repeated three times to facilitate user choice and attendance. Three special interest groups are developing user recommendations for future directions in the areas of Molecules, Modeling, and Statistics.

A Symposium on Mathematical Modeling of Circadian Systems was held on June 21, 1981, in conjunction with the annual meeting of the Association for the Psychophysiological Study of Sleep in Cape Cod, Massachusetts. The symposium reviewed strengths and weaknesses of various proposed mathematical models of the circadian timing system in predicting periodic biological phenomena.

A workshop on the current state-of-the-art of mathematical modeling in the biological sciences was held July 9-10, 1981, at the Uniformed Services University of the Health Sciences, Bethesda, Maryland. The major computer-based modeling systems in use today were reviewed. The future of mathematical modeling was discussed as well as optimal techniques for the solution of modeling problems. The PROPHET Network was discussed as a potential vehicle for a national modeling resource for biological sciences.

A workshop on technology in support of biomedical research was held at Johns Hopkins University, Baltimore, Maryland, July 30-31, 1981, and August 20-21, 1981. The first session of the workshop defined the problems, obstacles and impediments to application of new technology to biomedical research. The second session examined the various solutions to the defined problems which involved recommendations to NIH on how to enhance and exploit new technology in biomedical research.

BRP showed an exhibit featuring the Resource Directory and Program Guidelines at the Federation of American Societies for Experimental Biology meeting, Atlanta, Georgia, April 13-17, 1981, and at the Fourth Symposium on Computer Applications in Medical Care, November 2-4, 1980, Washington, D.C.

Use of Biotechnology Resources

One of the primary measures of accomplishment that can be applied to BRP is the extent to which its sponsored resources assist the various NIH categorical programs. With their cadres of highly skilled staff scientists and their

specialized and often unique facilities, Biotechnology Resources are frequently the scene of productive encounters between experts in a given technology and experts in a given biomedical discipline. Table I gives additional insight into the breadth and depth of this Program on the health research supported by Public Health Service (PHS). Table I lists the number of PHS grants that made use of Biotechnology Resources and awarded dollars to these grants. The distribution of research assisted by the BRP reflects in part how apportionment of research funds to the NIH Institutes and other agencies is made.

The total number of projects conducted in Biotechnology Resources and the number of investigators which made use of Biotechnology Resources are given in Table II for Fiscal Years 1979 and 1980. The number of publications resulting from research projects conducted in Biotechnology Resources in Fiscal Years 1979 and 1980 are also given in Table II.

Research Accomplishments

Biomedical Computing

Computer Processing of Visual Field Data - The visual field is a spatial map of the eye's sensitivity. Examination of the visual field in human subjects plays an integral role in the diagnosis and management of ocular and neurologic diseases. Visual field data, however, represent graphic patterns that must be interpreted qualitatively by trained observers and must be stored in patient records as relatively complex hand-drawn images. The complexity of these graphic images has inhibited their inclusion in automated record-keeping systems. In addition, although the data represent three-dimensional structures, they must necessarily be recorded as two-dimensional images on paper charts.

The Resource at Washington University has designed and constructed a microprocessor controlled recording device that has been interfaced to a standard clinical perimetric instrument. This device is now in use in the Department of Opthamology and allows the recording of the results of all visual field examinations. The recorded examinations are stored locally on small flexible disks which may themselves be included in the patient's physical charts. In addition, the data are also transmitted to a larger visual-field database system contained within a minicomputer system in the Department of Opthamology.

The assembled visual-field database may be used to retrieve patient records for immediate examination and may also be searched cross-sectionally for statistical analyses. Such a capability greatly enhances our ability to assess therapeutic interventions designed to forestall vision loss. Graphic image generation takes place at cathode ray tube display terminals as well as through a hard-copy plotting device. The three-dimensional nature of the data can now be exploited through the use of display algorithms that project three-dimensional surfaces as two-dimensional images using perspective and superposition of image elements to produce the desired visual effect. This process, in turn, promises to produce a truly fundamental advance in the technique of visual field examinations, allowing a more detailed study of specific forms of visual field defects and thereby improving our understanding of pathophysiological events which lead to blindness. The development of this perimetric system has been the result of a close collaboration between the Department of Opthamology and the Biomedical Computer Laboratory.

TABLE I
PHS Support for Investigators
Using Biotechnology Resources for FY 1980

NIH Institutes	Number of Grants	Awarded Dollars in $1,000
Aging	6	724
Allergy and Infectious Diseases	44	4,130
Diabetes, Digestive Diseases and Kidney	149	15,066
Cancer	171	19,127
Child Health and Human Development	42	4,418
Dental Research	7	472
Environmental Health Sciences	17	3,337
Eye	43	3,799
General Medical Sciences	299	32,592
Heart, Lung and Blood	127	21,084
National Library of Medicine	7	1,171
Neurological and Communicative Disorders and Stroke	52	4,918
Fogarty International Center	5	106
Division of Research Resources	22	3,924
Total NIH	991	114,867
Other PHS Components		
Alcohol, Drug Abuse and Mental Health Administration	36	3,158
Health Resources Administration	4	461
Center for Disease Control	1	128
Food and Drug Administration	1	24
Office of Health Research, Statistics and Technology	4	423
Total PHS	1,036	119,038

TABLE II

	FY 1979	FY 1980
Number of Projects	1,421	1,346
Number of Investigators	2,088	2,180
Number of Publications		
Papers	863	829
Books	87	76
Abstracts	232	241
Total	1,182	1,146

Computer Graphic Studies of Anti-Cancer Drugs - In collaboration with Dr. Corwin Hansch (Pomona College) the Resource at the University of California, San Francisco, has explored one of the most powerful classes of anti-cancer drugs, those which inhibit an enzyme which produces precursors to DNA. The enzyme is dihydrofolate reductase and a typical drug is methotrexate, effectively used for some years in cancer chemotherapy. Dr. Hansch has studied this system for some time in attempts to design more potent drugs with less toxic side effects. He began studying the three-dimensional structure of the enzyme but found that the molecular models available were too clumsy and inaccurate for the precise fits between drugs and receptor that he needed to study. Beginning in the spring of 1980, he and his postdoctoral associates have collaborated with the Computer Graphics Laboratory in studies of the binding of series of related compounds. This in turn is leading to new syntheses and eventually to new drugs for possible use in the treatment of cancer.

The Formation of Specific Connections among Nerve Cells - It is generally believed that for the brain to function in a correct manner nerve cells must be connected to each other in a very accurate manner. This means that during the development of the brain, each nerve cell must be able to find the correct ones with which to form such connections. In order to find out how a cell does this, and what factors can affect its ability to achieve its normal goal, it is important to determine what events occur during development. For example, does a cell always make the appropriate contacts at first, or is there a period of trial and error, of searching around, until the right targets are found? Furthermore, will a cell form other connections if its normal targets are missing, and with whom? And lastly, to what degree are the connections specified by the genes of the organism, and how are they modified by environmental factors like chemicals, temperature, radiation and so on?

Although in the long run the Resource at Columbia University is interested in the development of connections in the human brain, much simpler nervous systems are studied because they are more accessible to a complete understanding of their structure, function and development. Thus, a very small invertebrate is being studied and then only part of its brain. This part contains a few hundred cells, which have been mapped in detail, both in the adult and at various embryonic stages using the CARTOS computer imaging system. This group of nerve cells is understood rather well, and models have been proposed for the development of its particular connections. In recent work it has been shown, using a microbeam to destroy or alter certain cells instruct others as to their fate, and trigger their development. Thus, it has been shown that the problem of development is not "simply" one of autonomous cells finding other particular autonomous cells to connect to, but that the cells themselves are defined by who they contact. It is expected, therefore, that factors that affect the interaction of cells in development would lead to the formation not only of abnormal connections, but also to the making of unusual or abnormal cells.

GENET - An Experiment in Artificial Intelligence (AI) System Dissemination - The MOLGEN project at Stanford has focused on applications of artificial intelligence and symbolic computation to the field of molecular biology. The research began in 1975 and is currently in the first year of a three-year grant renewal. In early 1980 it was realized that some of the systems developed by MOLGEN were of direct utility to many scientists. Accordingly, with the cooperation of the SUMEX-AIM staff and close coordination with the AIM Executive Committee, it was decided in February 1980 to provide a carefully limited guest service for

the community use of such systems. Two programs, SEQ and MAP, were made available to the national academic community. SEQ is a general purpose nucleic acid sequence analysis system and MAP is a program which determines restriction sites from enzymatic digest data. Investigators have free dial-up access from almost anywhere in the United States to these capabilities. Over 300 researchers at over 80 institutions have used this service. There were two major reasons for the establishment of this guest service, which took the form of the GENET account on SUMEX. The first was to broaden MOLGEN's base of scientist collaborators, to find molecular biologists at institutions other than Stanford who could contribute actively to our knowledge-based approach to problem solving. The second was to introduce a generally computer-naive community to the benefits of resource sharing provided by a system like SUMEX, with the hope of serving as a model for the dissemination of other AI software and possibly for an eventual resource for molecular biology.

GENET has been important both for MOLGEN and for the national community (over 200 users) of molecular biology. It has ensured a steady flow of ideas for the artificial intelligence research that is core to both the MOLGEN grant and the SUMEX-AIM mission. It has also provided a useful service to an international community that is not readily available elsewhere.

The University of Washington/Northwest Consortium - Substantial progress toward an industry-university consortium supporting the design of very large scale integrated (VLSI) circuitry, the next wave of the burgeoning microelectronic industry, has been made recently. Each of several industrial members of the consortium will advance $50,000 start-up funding and commit to yearly dues contributions. The biomedical research computing of our collaborators will certainly benefit from the application of VLSI technology. This University of Washington Resource will draw upon its substantial experience with biomedical laboratory automation to apply VLSI advances.

This activity brings closer a date when we can be developing VLSI systems for medical uses. The start-up costs for VLSI work are far beyond the monies that NIH can expect to expend. This Resource is trying to utilize industrial and Defense Advanced Research Projects Agency funds to accomplish the start-up without asking for direct funding from NIH. When it is ready for production of specific biomedically justified projects, it will submit grant requests via the usual channels to support this activity. This may occur as early as next year.

Biomedical Engineering

Potassium Sensor - The Biomedical Electronics Resource at Case Western Reserve has undertaken a potassium sensor collaborative project with Abbott Laboratories in Chicago. Abbott Laboratories provides a biochemist, a mechanical packaging engineer and an electronics engineer for final advanced development who work directly with the Resource staff. The proposed sensor is hand-held and disposable. Abbott will provide the evaluation data, packaging and will construct the instrumentation. IC Engineering of Arizona will fabricate the sensor's electronics. The Resource will do the feasibility studies and supply the technological know-how.

Biological Structure and Function

Nanosecond Spectroscopy - The facility of the Center for Fast Kinetics Research (CFKR), University of Texas, is being used by an investigator from the University of Texas to map label sites in ribosomes. The technique utilizes the fact that pairs of photo-activated molecules having the proper characteristics can interchange energy across space. The effectiveness of this energy transfer depends on the distance between fluorescent probe species. The CFKR Resource can provide precise measurements of fluorescence lifetimes in the region of one nanosecond and have been used to obtain measurements between probes attached to the S1 protein of the small ribosomal subunit and to the 3'-end of 16S RNA. Experiments with probes attached to several other locations are in progress.

Spin Label-Oxygen Methods - Scientists at the Biomedical Electron Spin Resonance (ESR) Spectroscopy Center, Medical College of Wisconsin, have developed a new method for measuring oxygen concentration in biological systems using nitroxide radical spin labels as molecular probes. The interactions of oxygen and nitroxide radical spin label cause changes in the ESR characteristics of the spin label that permit determination of the biomolecular collision rate between the two. This rate depends upon the product of the oxygen concentration and the oxygen diffusion constant. The rate of change of the biomolecular collision rate when nitrogen rather than air is suddenly flowed over the sample cell depends on the concentration of oxygen in the sample cell, independent of the diffusion constant. This method is being applied to measurement of oxygen concentrations in liposomes. Other related spin label-oxygen methodologies are being developed.

High Frequency Nuclear Magnetic Resonance (NMR) - Regular scheduling on the 500 MHz NMR spectrometer at the National NMR Facility for Biomolecular Research, Massachusetts Institute of Technology, began in October. The instrument includes a variable temperature probe, high precision temperature control and a sensitive deuterium lock channel. The spectrometer, because of its ease of use and the extensive repetoire of pulse experiments which can be performed, has found great favor with users. Initial studies have included a project on proton nuclear Overhauser effects and protein dynamics in lysozyme, a study of carbohydrates using two-dimensional NMR experiments, and several projects on solution conformations of macromolecules.

The Action of Lithium on the Nervous System - Lithium is an effective treatment for many patients with manic depressive illness, reducing the extremes of mood which characterize that disorder. It is also reported to be effective in the treatment of certain somatic illnesses, for example, hyperthyroidism and granulocytopenia. In addition, a wide range of psychiatric and non-psychiatric nervous conditions, from impulsive aggressiveness to movement disorders, have responded in varying degrees to lithium treatment. There is concern over all of these therapies, since chronic treatment with lithium may cause kidney damage. In none of these therapies is it clear how lithium is exerting its effects, or whether the effects are related. In spite of that, many physiological and biochemical actions of lithium are known, even though their basic relationship to disease and therapy is still unclear. The mechanism of action of lithium is being investigated in the mass spectrometry resource at Washington University, St. Louis, Missouri, and the toxicity aspects of the drug are being studied at the mass spectrometry resource at Rockefeller University in New York.

A major effect of lithium on inositol metabolism in the cerebral cortex has been investigated by Dr. William Sherman in the Psychiatry department at Washington University. Inositol is a vitamin-like substance, since body requirements are sometimes met by diet, although at other times it is made in the body from glucose. In the nervous system, some of the inositol is found as a structural part of certain specialized fatty substances called lipids. These lipids, the phosphoinositides, undergo increased breakdown and synthesis during the transmission of nerve impulses, thus appear to have a role in the function of the nervous system.

Several years ago Dr. James Allison and Dr. Sherman found that lithium treatment causes inositol levels to decrease in the cerebral cortex of rats. The decrease is remarkable, a 30% loss at high doses. More recently, it was found that a metabolite of the phosphoinositides, an inositol phosphate, increases several-fold in concentration while the free inositol is decreasing. This suggestion that lithium interferes with phosphoinositide function is strengthened by another finding, that lithium blocks the activity of the enzyme which converts inositol phosphate to free inositol. Thus, lithium may change the normal levels of these metabolites in tissues, thereby modifying nerve impulse transmission. Whether this hypothesis is true is under active study. It provides some hope that we can obtain insight into the way lithium acts in manic-depressive illness and other disorders.

Lithium has two naturally occurring isotopes, ^{6}Li and ^{7}Li. Human and animal studies indicate that the distribution and toxic effects of Li are isotope specific. Lithium toxicity appears to be due to ^{6}Li but it is not known which isotope is responsible for the therapeutic effects of lithium. Dr. Frank Field of the Rockefeller University is collaborating with Dr. P.E. Stokes of Cornell Medical Center and Dr. F. Brink of Rockefeller University to develop a mass spectrometric method to assay lithium in cells and fluids from manic depressive and control patients.

Both of these studies could lead to a better understanding of the therapeutic and toxic effects of lithium in manic depressive patients. They could also lead to individualized lithium treatment regimens for different patients and indicate ways of avoiding lithium toxicity.

Fiscal Year 1981
Annual Report
General Clinical Research Centers Program Branch
Division of Research Resources

Program Description

During the past year the General Clinical Research Centers (GCRC) Program celebrated its 20th Anniversary. The continued scientific productivity of the Program has amply demonstrated the wisdom of Congress, which in 1959 directed the NIH to establish clinical research centers throughout the country to improve and intensify the scientific attack on human diseases and their basic biologic parameters. As a part of the 20th anniversary celebration, Centers throughout the nation have sponsored seminars by leading clinical scientists and hosted a series of special events for their congressional representatives and the public. This spring, the Director of NIH gave special recognition to the success of the Centers in an address to the national clinical research societies.

Advances and accomplishments in the biomedical sciences have been quite remarkable in the past 20 years, and are documented in various NIH publications. During the past year, the GCRC program, as part of its 20th anniversary activities, has undertaken to document the role of the program in these advances. The initial effort by the Centers has produced a bibliography of more than 6,500 key scientific articles, classified by scientific area. Four areas, including the neurosciences, diabetes, hypertension, and neonatology, have been selected for special reports. Committees have been established in each area to review and document the role of the program in contributing to advances in these important areas of public health.

The CLINFO program has been expanded to several new sites, including Scripps Clinic, Columbia University, and the University of Iowa. These data management resources continue to enjoy a favorable reception from the clinical research community. Individual CLINFO sites have begun to enhance research activities through sharing of information and programs.

The Clinical Associate Physician (CAP) Program has received increasing recognition from NIH as a means of meeting a critical need to attract physicians to careers in clinical investigation. Of former CAPS, more than 90% have entered academic medicine and 50% of these have already successfully competed for NIH grants or contracts.

Typical Center and Program Changes

The typical Center in Fiscal Year 1981 contained 8 beds, staffed by twenty full-time personnel, at a cost of $839,000 (Table I). The program appropriation has grown from $35 million in Fiscal Year 1970 to

$60.148 million in Fiscal Year 1981 (Table II). Although appropriations have not kept pace with the costs of operating the Centers, and the number of beds has decreased, the use of the Centers for research outpatient visits has steadily increased. The productivity, as measured by numbers of publications and abstracts, has shown steady growth over this period.

Table I

ESTIMATED TYPICAL CENTER
(75 Centers)

Funded Fiscal Year 1981

8 Beds

PERSONNEL	FTE	AMOUNT (thousands)
Professional	1.1	$ 65
Administrative	1.4	24
Laboratory	2.4	45
Dietary	3.1	47
Nursing	11.7	216
Other 1/	.9	22
Fringe Benefits (19.5%)		82
	20.6	$501
HOSPITALIZATION		
Routine/Per Diem/Scatter Bed		$246
770 B Patient Days X $105		(81)
327 C Patient Days X $105		(35)
1469 A Patient Days X $60 (Ancillaries)		88
1165 Outpatient Visits X $22 (Ancillaries)		26
		$244
TRAVEL		1
SUPPLIES, EQUIPMENT, OTHER		37
TOTAL DIRECT COST		$783
INDIRECT COST (7% of the Total Direct Costs)		56
	TOTAL	$839

1/ Includes 37.62 FTE Clinical Associate Physicians positions.

TABLE II

GCRC PROGRAM, 1969 - 1981

FY	CENTERS	POSITIONS FTE	FUNDED BEDS	PATIENT DAYS A & B & C	OUTPATIENT VISITS	APPORTIONMENT (in thousands)
69	93	2,298	1,023	245,943	---	$ 35,004
70	93	2,076	904	244,824	1,175	35,004
71	82	1,885	881	234,870	14,515	38,004
72	84	1,867	907	238,152	23,654	42,181
73	83	1,790	893	227,501	36,280	41,300
74	87	1,795	877	232,534	50,614	42,320
75	84	1,732	823	223,269	50,020	42,619
76	84	1,727	784	222,488	56,217	42,533
77	82	1,679	755	204,369	65,130	47,283
78	79	1,706	633	193,151	71,049	51,946
79	74	1,622	613	198,000	86,215	51,941
80	75	1,694	602	195,880	101,216	56,720
81	75	1,547	593	186,958(est.)	87,395(est.)	60,148

HIGHLIGHTS OF THE GCRC PROGRAM FY 1981

PATHOGENESIS

Paget's Disease

Paget's disease of bone is a common, painful disorder of aging. Drugs and surgery are used as treatments, but curative therapy can only be developed when the cause of the disease is discovered. Efforts in this direction have been stimulated recently by the finding of virus-like structures in certain bone cells of patients with Paget's disease. Evidence has been obtained for the presence of a respiratory syncitial virus or some related agent in these cells. If the virus can be isolated and used to produce bone disease in an experimental animal, thus proving the virus to be the cause of the disease, the findings could serve as the basis for a new approach to the treatment and prevention of this significant public health problem.

Uremia

Patients with chronic kidney failure have abnormalities in the functions of the nervous, musculoskeletal, blood forming, and reproductive systems. These derangements have for generations been thought to be due to a toxin or toxins in the blood of patients, but these have never been identified. During the last few years evidence has accumulated that parathyroid hormone is one major uremic toxin. Since the state of excessive parathyroid hormone concentrations can be prevented or treated, this finding opens the way to treatments which could ameliorate the uremic syndrome.

Prostatism

Enlargement of the prostate, which obstructs the outflow of urine and can cause infection and kidney damage, is a nearly universal change in aging men. It is known that testoterone from the testes must be present for prostate enlargement to develop. Recent work provides a basis for understanding this important disorder. Aging men show an impaired ability to metabolize dihydrotestosterone (DHT), formed in the body from testosterone. DHT is a growth hormone for the prostate. This work not only provides an understanding of the pathogenesis of prostate enlargement, but suggests possible new therapies based upon control of the enzymes which control synthesis and degradation of DHT.

Hypoglycemia

A series of studies, some involving collaboration between several CRCs, has demonstrated that the hormone glucagon plays a primary role in recovery from hypoglycemia (low blood sugar), that epinephrine largely

compensates for deficient glucagon secretion, and that recovery from hypoglycemia does not occur in the absence of both glucagon and ephinephrine. Patients with insulin-dependent diabetes mellitus (IDDM) have blunted glucagon responses, and are dependent on ephinephrine action for recovery from hypoglycemia. There are important practical implications to these findings, as antagonists to some of the actions of epinephrine are commopnly prescribed for disorders, such as hypertension and agina. If given to patients with IDDM, these agents could put these patients at risk for serious hypoglycemia.

Alzheimer's Disease

Recent evidence suggests a familial occurrence of Alzheimer's disease, a mental deterioration beginning in middle life. Moreover, an excess frequency of Down's syndrome (mongolism) has been found among the relatives of patients with Alzheimer's disease. These observations support the hypothesis that Down's syndrome and Alzheimer's disease have related genetic defects, and suggest that Down's syndrome should be considered as a prenatal diagnosis in pregnant women with a family history of Alzheimer's disease.

Alport's Syndrome

New data indicate that at least 1% of renal failure in males in the Rocky Mountain region of the United States is accounted for by hereditary nephritis ("Alport's Syndrome"). A biochemical marker, "hereditary nephritis protein", has been found in the urine of these patients, and seems to be identical with C3bi, part of the complement system involved in fighting infection. This and other evidence suggest that hereditary nephritis may be a defect of complement metabolism.

Photosensitivity

A circulating photoreactive factor has been found in some patients who are very susceptible to the ultraviolet component of sunlight, developing hives and wheals after exposure. Current studies are attempting to identify this factor.

Diabetes

Some new information has been obtained about the occurrence and management of complications in children with diabetes mellitus. A high percentage of newly diagnosed diabetic children have significant alterations in the electroencephalogram, and in some of these the alterations persist for as long as a year. Also, 60% of adolescents with diabetes for more than six years have signs of minimal retinopathy. Too-rapid correction of metabolic abnormalities in teenagers with longstanding diabetes under poor control may precipitate rapid deterioration in the eye condition.

PREVENTION

Hyperthermia

Certain patients develop musculoskeletal rigidity and very high body temperature (malignant hyperthermia) when exposed to some anesthetic agents. Two groups of susceptible individuals, belonging to families in which the condition seems to be inherited, have been identified on the basis of metabolic responses of muscle biopsy specimens. These studies open the possibility of developing a screening test which could predict the risk of malignant hyperthermia, preventing this possibly lethal complication of routine anesthesia.

Renal Stones

Pregnancy results in the transfer of large amounts of calcium from mother to fetus. Maternal calcium supplementation is widely practiced. In recent years, it has been recognized that maternal calcium absorption in the GI tract increases in pregnancy, and that this is due to placental production of 1,25 dihydroxy-vitamin D. Now the first prospective systematic study of mineral metabolism has shown that urinary calcium excretion and 1,25 vitamin D levels are markedly elevated in pregnant subjects. This is analogous to the common renal stone-forming state (absorption hypercalciuria) and suggests that calcium supplementation in pregnancy is unnecessary and probably dangerous.

DIAGNOSIS

Breath Tests

Analysis of the breath has been attracting increased interest as a non-invasive, accurate method of diagnosing systemic diseases. The recently-developed xylose breath test, for example, has a 92-95% reproducibility in the diagnosis of malabsorption, compared to 35-38% for bacterial culture of the intestine, previously the best method. The breath test also does not have the high false-negative rate or the demanding technical requirements of the culture method. A breath test has also been used to identify cirrhosis in narcotic addicts who are being maintained on methadone. This is important because methadone metabolism may be significantly altered in patients with liver disease.

Deafness

An automated system has been developed to measure changes in body movement following an auditory stimulus, for use in detecting hearing loss in neonates. This non-invasive, portable device has a small false-positive error and a negligible false-negative error.

Black Lung Disease

A relatively simple, non-invasive diagnostic test, total respiratory resistance mesured by the forced oscillation technique, can be used as an indicator of early stages of soft coal miners' pneumoconiosis.

Short Stature

A recently developed assay system allows the reponsiveness of patients to growth hormone to be measured by a test of their blood cells in culture. With this test it was demonstrated tha the rare form of short stature known as Laron dwarfism is due to a lack of tissue responsiveness, rather than to a deficiency of the hormone. This is the first such clinical application of a tissue culture assay known, and it opens up the opportunity of determining the hormonal responsiveness of a patient without the need to actually inject hormone and do complex physiologic studies. Follow-up studies indicate that the responsiveness of tissues to insulin can also be assayed by the tissue culture method.

THERAPY

Hypercalcemia

Hypercalcemia (elevatd blood calcium) is a common complication of certain malignancies, especially multiple myeloma and metastatic breast and lung cancer. It causes great morbidity and significant mortality. In a series of 12 patients with this disorder, it was found that a new drug called dichloromethylene diphosphonate (Cl_2MDP), which inhibits bone resorption but not mineralization of new bone, returned serum calcium to normal levels in 11 of them. There was no evidence of significant toxicity. This study suggests that Cl_2MDP may be of major value in the management of this serious clinical problem.

Iron Toxicity

Long-term transfusion therapy is commonly used for anemias of chronic disease, such as the hereditary anemias. This therapy is effective, but leads to a cumulative, toxic body burden of iron, which has been assumed to be significant only after many years. However, recent studies have demonstrated damage to heart, lungs, and endocrine glands after even short-term therapy (months). This is important because it means that therapy with the subcutaneous infusion of desferrioxamine, a drug which can bind iron and remove it from the body, should begin early.

Heart Irregularities

Although certain kinds of arrhythmias are benign in normal children, they often presage sudden death in children with abnormal hearts. The usefulness of phenytoin in the treatment of ventricular dysrhythmias in

children has been demonstrated by successful treatment in 95% of those with abnormal heart conditions. A new dosage regimen has been developed which reduces the length of time required for effectiveness from one week to two days.

Tourette's Syndrome

Basic studies in this Clinical Research Center have indicated that Tourette's syndrome, a disability of mental development, is much more common than previous thought. An elucidation of the steps in its neurochemical pathology has led to a new medical approach. Clonidine, a centrally acting drug which affects norepinephrine metabolism, has been shown to ameliorate symptoms of Tourette's syndrome in many patients who were previously unresponsive or unable to tolerate the standard medical approach, haloperidol.

Failure of Maturation

The open-loop pump developed for the continuous subcutaneous infusion of insulin into diabetics is proving to be of use in other disorders as well. For example, the pulsatile delivery of growth hormone is effective in the treatment of hypogonadotropic hypogonadism, a pituitary disorder which prevents normal adolescent maturation. Long-term studies of nocturnal pump-delivered pulses of hormone are now underway in this disorder.

Cancer Treatment

A totally implantable drug delivery system for regional cancer chemotherapy is being used with striking success. The system delivers high concentrations of cancer-fighting drugs directly to the tumor site without causing the degree of systemic toxicity and side effects typical of conventional chemotherapy techniques. The response rate for hepatic tumors, for example, has been 85%, four to five times the rate with conventional chemotherapy. Continuous drug delivery to the tumor area is achieved by a small infusion pump secured in a pouch just under the skin. For treatment of liver cancer, a small catheter leads from the pump directly into the hepatic artery.

Chronic Pain

Unlike acute pain, which warns of tissue damage, chronic pain serves little useful biological function. It can cause sufferers to seek repeated surgery and to risk narcotic addiction in search of relief. Now electrostimulation of the brain by a pocket-sized device enables certain pain victims, some of whom were previously invalided by their pain, to lead lives free of pain and drug dependency. The FDA-approved device stimulates the periqueductal region of the gray matter of the brain, causing it to release beta-endorphin, a normal brain compound with pain-masking effects.

Short Stature

Until recently it was thought that only growth hormone-deficient children could benefit from growth hormone (GH) treatment. It is now known, however, that injections of GH can increase the stature of some short children with normal levels of GH. Together with the recent production of GH by recombinant DNA technology, this finding opens exploration of clinical possibilities such as treatment of short stature accompanying juvenile rheumatoid arthritis, Turner's syndrome, and other disorders, as well as more rapid repair of wounds, bones, and cartilage.

Trauma

A series of GCRC studies has led to significant practical contributions to decreasing the morbidity and mortality in severe trauma, the leading cause of death in young people. For example, the administration of ethacrynic acid to reduce swelling of cerebral gray matter reduces the mortality rate and improves the functional level in patients with severe isolated closed head injury. Also, it has been shown that the common practice of using drugs to paralyze patients who are being mechanically ventilated with positive end-expiratory pressure if they make inspiratory efforts reducing airway pressure, is not necessary or even desirable. In a similar way, it has been shown that patients who require respiratory support should not be removed from end-expiratory pressure to breathing through an endotracheal tube at ambient end-expiratory pressure (T-tube test). The data suggest that endotracheal intubation should be accompanied by low levels of continuous positive airway pressure, and patients should be extubated directly from there. Another example is the demonstration that injured patients who require endotracheal tubes do better if they receive continuous positive airway pressure (if they are breathing spontaneously) or positive end-expiratory pressure (if they are not).

Hypertension

Captopril, an angiotensin converting enzyme inhibitor, is an effective drug for the treatment of hypertension, but it has recently been found to have a high incidence of side effects and a high rate of hypersensitivity. A new, chemically-similar angiotensin converting enzyme inhibitor, MK-421, has been found in preliminary studies to be equally effective, and to have a higher potency and longer duration of action, permitting use of much smaller doses and causing many fewer side effects.

Hyperlipidemia

Recent studies have led to a liberalization of dietary recommendations for patients with hyperlipidemia. Shellfish, previously eliminated from diets for these patients because of the high cholesterol content, may be consumed in amounts of up to three ounces per day without

affecting the cholesterol level. Moreover, the consumption of up to six to eight ounces of fish per day may have a significant lipid-lowering effect. These findings have practical importance in adding to the palatability of diets for hyperlipidemia.

Renal Osteodystrophy

Renal osteodystrophy, characterized by failure to grow, bone pain, bone deformities, and frequent fractures, is the most important complication of chronic kidney failure in children. Conventional vitamin D therapy is often unsuccessful and frequently causes hypercalcemia (toxic elevation of blood calcium). The osteodystrophy has now been found to be a heterogeneous disorder, occurring in several forms; to develop even in patients with only mild or moderate chronic renal failure, at a time when their clinical examinations, blood studies, and x-rays are normal; and to respond in most ways to the administration of the vitamin D metabolite 25-hydroxyvitamin D_3, with a negligible incidence of hypercalcemia.

Infertility

The drug clomiphene and intranasal luteinizing hormone-releasing hormone (LHRH) were used to induce ovulation in eight chronically anovulatory patients who were under treatment for infertility. All had failed to ovulate in response to clomiphene even when the drug was given in combination with human chorionic gonadotropin in therapy. Clomiphene, 100 mg. per day, was given on days five through nine of the menstrual cycle and synthetic LHRH was administered intranasally from day 11 to day 14 to induce late follicular development and ovulation. Five of the eight patients ovulated and three of these conceived. Combination therapy with clomiphene and intranasal LHRH offers a new means to treat anovulatory infertility.

Obesity

Two studies have indicated undesirable side effects of the low calorie, high-protein carbohydrate-free diet. Endurance was markedly reduced, muscle glycogen was not spared, and visceral proteins were reduced in subjects on this diet as compared to those ingesting a small amount of carbohydrate. In the markedly obese diabetic on a low calorie diet, nitrogen retention is significantly better if the diet contains carbohydrate. On the other hand, exercise capability is not impaired on a carbohydrate-free diet of normal caloric content.

Red Cell Aplasia

The human bone marrow disease, pure red cell aplasia, has been found to be of immunologic origin. Many patients with this disorder have an antibody that inhibits blood formation and is toxic to developing red blood cells. This finding has led to a rational therapy, administration of the immunosuppressive drugs prednisone and cytoxan.

About 60% of patients with red cell aplasia respond to this regimen with a remission of their disease and a discontinuance of the need for red cell transfusions. Most recently, it has been shown that children with transient erythroblastopenia, a disease which resembles pure red cell aplasia, also have an antibody that inhibits red cell development.

Chronic Asthma

Patients with chronic asthma are generally treated first with theophylline, cromolyn, and bronchodilators. A few patients, whose symptoms are not adequately controlled with these medications, require continuous use of corticosteroids to relieve chronic debilitating symptoms and to decrease the frequency of recurrent hospitalizations and emergency room visits. The value of maintaining the initial drug therapy in steroid-dependent asthma has been questioned, but recent work has shown that continuing bronchodilator therapy with theophylline when giving steroids increases the number of symptom-free days, decreases the need for other drugs, markedly lowers the amount of supplemental steroids needed, and improves pulmonary function and exercise tolerance. The results prove that maintenance bronchodilator therapy with theophylline can provide clinically important benefits for patients with steroid-dependent asthma.

Laryngeal Papillomatosis

Papillomatosis is a potentially life-threatening proliferative disease of the larnyx, thought to have a viral etiology. Repeated surgery may be required. The synthetic drug polyinosinic, polycytidilic acid stabilized with polylysine (poly ICLC), an inducer of the antiviral agent interferon, has been tried in three patients with this disorder. A five-fold decrease in the frequency with which surgery was required ensued. These results strongly suggest that additional studies of antiviral agents in papillomatous diseases may be rewarding.

Immune Deficiency Diseases

A safe and effective immune globulin preparation is needed for intravenous use. A preparation of modified (reduced and alkylated) immune globulin has been found to be safer, much less productive of side effects, and overwhelmingly preferred by patients, when it is formulated in 10% maltose. This simple change in the formulation of antibody will allow the rapid infusion of large doses of immune globulin, thus improving the management of patients with antibody-deficiency diseases.

Medical Advances

The GCRC Advisory Committee and staff have initiated a review of the role of the Centers in the medical advances of the last twenty years.

As a first step, the Committee and GCRC Program Directors listed some of the important advances in medicine since 1960, and divided them into 32 categories and 254 subcategories. The Program Director of each Center was asked to list its most significant publications in these subcategories. To date, a bibliography of more than 6500 related articles has been compiled. Four major categories were selected by the GCRC Committee for the initial studies: neuroscience, diabetes, hypertension, and neonatology (including immunology). A draft paper on the neuroscience has been presented to the Director, NIH for review. A paper on GCRC contributions to advances in diabetes has been drafted and is currently undergoing editing. Plans have been made for committee to sudy hypertension and neonatolgy during the coming year. When the project is completed, the role of the GCRC program's progress in many areas of great importance to public health will be clearly documented.

CLINFO

During the past fiscal year, six production versions of the CLINFO System were installed (University of Cincinnati, Yale University, Mayo Foundation, Peter Bent Brigham Hospital, University of Minnesota, Scripps Clinic). The CLINFO System, a computer-based data management system, was specifically developed for the clinical investigator. Testing of three prototype systems at Baylor University, University of Washington and Vanderbilt University was completed by June 1977, and the results revealed that the system was acceptable to the clinical investigator and that it would be a useful data-management tool. Bolt, Beranek and Neuman, Inc. (BBN) was competitively selected to be the commercial purveyor. The first production systems were installed at Duke University and Johns Hopkins University in late 1978.

Each of the production versions of the CLINFO System, except one, has been heavily used, averaging an estimated 5215 connect hours per week. The CLINFO software can now be used unaltered on several Digital Equipment Company (DEC) computers, thus allowing use of a smaller, less expensive two-terminal version of the System; a grant for one smaller system has been awarded and will be evaluated. Enhancements continue to be made in the software, an important one being that the maximum number of patients per study has been increased from 300 to 5000, which should accommodate all but the largest clinical trials. The position of System Managers under the direction of the CRC was proven critical to the success of the CLINFO project.

The second annual meeting of the CLINFO System Managers took place in April 1981. There was more participation at this meeting by the System Managers who manage the production version. The occasion provided a valuable opportunity for them to exchange experiences and ideas with each other and with representatives of BBN and NIH. The meeting was highlighted by the establishment of a CLINFO System Managers Organization and selection of its Charter Committee. In addition to an annual meeting, the System Managers can also communicate their ideas and problems through the CLINFO Newsletter.

Installation of each new CLINFO System has gone smoothly. This has been helped by Dr. Howard Thompson, who is an experienced CLINFO user and Clinical Professor and who is under contract to the GCRC Branch to assist investigators and the System Managers with installation of a new CLINFO System. The purveyor, BBN, has also been successful in responding to problems providing excellent maintenance of the production versions, and improving the software by issuing new versions which incorporate user suggestions.

The future of CLINFO will be determined by periodic meetings of CLINFO Advisors reporting through the CRC Advisory Committee. Such a group was convened recently to advise the GCRC Program on the future course of CLINFO and related data management problems. It made several recommendations: 1. The GCRC Program should examine very closely the suitability of Centers for CLINFO, particularly making certain that control and direction of the CLINFO System reside with the Center and the users. 2. The System Manager should continue to be an integral component of the system. 3. In order to have better estimates of CLINFO usage, a transaction log program be added to the software. 4. The System Managers should design a plan to document the need for advanced statistical capabilities. 5. The BIOINFO proposal of the Biotechnology Program to produce software that will make it possible to run CLINFO on a variety of computer hardware should be encouraged. 6. The group and the Program should further explore the usefulness of PROPHET as a data management resource.

Clinical Trials

The Contract: "Evaluation of the Role of Clinical Research Centers in Clinical Trials with Emphasis on Information Processing" was awarded to the Rand Corporation on September 30, 1978. The goals of this contract were to develop a broad understanding of clinical trials, their organizational, administrative, operational, and information processing problems, and potential solutions; and to develop a detailed understanding of the role of the GCRC Program in clinical trials and to recommend methods to facilitate trials which make use of the resource it supports.

The contractor visited carefully selected leaders and experts involved in the process of clinical trials, appropriate people from the staffs of clinical trials coordinating centers, leading clinical investigators from cooperating clinics and personnel at GCRCs involved in the performance of clinical trials.

The contractor found that the GCRCs surveyed had an average of 15 active clinical trials, and that half of the resources were used to support these trials. The typical interviewed director believed that clinical trials create problems in terms of ethics, resource allocations, and funding. Most directors believed that trials could be improved if there would be more outpatient facilities and improved

computational resources. Several directors saw a need for more laboratory technicians, social workers, and data collectors.

In their final report the contractor made the following recommendations:

Provide research data coordinators to support clinical trials.

Make biomedical scientists (e.g., biostatisticians and computer programmer/analyst) available in the GCRCs on a regular but limited basis.

Make the CLINFO data management and analysis system available to clinical trials that use GCRC resources.

Augment the functional capabilities of the CLINFO system to include analysis of covariance, improved data editing, document tracking, sample size determination and randomization.

Provide a computerized nutrition data base and diet calculation program for GCRC dietitians.

Provide fiscal management and word processing computer programs for GCRC administrative coordinators.

Explore methods to improve the quality of clinical trials by helping investigators to improve their practice of research methodology, statistics, and information processing.

These recommendations will be reviewed by the GCRC Advisory Committee this year. While resource limitations may prevent the implementation of many of these recommendations at this time, diffusion of CLINFO data management is proceeding as a high priority program goal.

A final report of the findings and recommendations has been printed by the contractor and has been distributed by the contractor to all GCRCs participating in this study and to all members of the 'Ad Hoc Advisory Committee of this contract. The GCRC Branch announced the publication of this report to all GCRC program directors who did not participate in the study (35) and all of these requested copies of the report. Copies of the report have been requested by a number of individuals inside and outside the NIH.

Clinical Associate Physician Program

A Clinical Associate Physician (CAP) is a young academic scholar, trained in patient care and research through the fellowship level or its equivalent, who is supported by GCRC investigation by working on a GCRC. By supplementing the professional level care of Center patients, providing Core Laboratory assistance, or performing supervisory or instructional duties, the CAP functions as an institutional resource while developing into an independent investigator.

The CAP program has been a successful one, and has attracted a large number of highly qualified applicants. To maintain the competitiveness of the program, the salary of a CAP has been increased from $25,000 to $30,000 (plus fringe benefits), and awards have included $5,000 per year for small equipment, supplies, computer time, and travel. Each grantee institution is to be permitted a maximum of two CAPs (three if there are separate Adult and Pediatric Centers). Budget constraints, however, have required that the GCRC Program no longer accede to requests for a third year of support for CAPs. The plan is to support as many meritorious candidates for two years as funds will allow.

The GCRC Program is currently supporting 46 CAPS, compared with 34 last year, and the number who have completed the program has increased from 42 to 55. Of these 55, 49 have obtained academic positions and 6 are in private practice. The typical "graduate" of the program spends 49% of time in clinical research, 15% in basic research, 27% of time in teaching, and 9% of time in practice. Although the program is relatively new (24% of those who have completed the program did so in the past year), 50% of the "graduates" in academic life have obtained NIH grant support.

The total cost of the CAP program in 1981 was $1.851 million.

Twentieth Anniversary of the General Clinical Research Centers

During this Fiscal Year, the General Clinical Research Centers (GCRCs) Program has been celebrating its 20th Anniversary with many activities across the country.

Most of the 12 charter GCRCs have been involved in a variety of special events ranging from endowed scientific lectures to reunions of former patients to public open houses.

Clinical Research Centers which have participated in 20th anniversary activities to date are located at the following academic medical centers: Washington University, St. Louis; University of Washington; Johns Hopkins University; Yale University; University of Pennsylvania; Duke University; Emory University; University of Rochester; Ohio State University; Vanderbilt University; and the University of Southern California.

A recent report to the Senate Appropriations Committee called GCRC's "a truly unique conduit for the transfer of information and technology from the laboratory bench to the bedside." The report concluded that this "invaluable and irreplaceable national scientific resource... (should) be significantly strengthened."

Last April, Dr. Donald Fredrickson, in one of his last public statements as NIH Director, spoke to delegates attending the clinical research meetings in San Francisco. He told participants: "The

clinical research centers are of very special importance. It's quite important to examine what they support--nearly 4,000 research investigators (working) on over 3,000 projects that are supported by the categorical institutes to the tune of nearly $270 million in NIH grants.

"It is around these Centers that we're all going to have to unite...to determine whether or not there are other savings in categorical funds that can be realized by maximizing the use of both (the) inpatient and outpatient facilities in clinical research centers."

Biomedical Research Support Program
Division of Research Resources

Annual Report
Fiscal Year 1981
October 1, 1980 - September 30, 1981

Biomedical Research Support Grant Objective:

To strengthen and enhance the research environment of institutions heavily engaged in health-related research through the use of flexible funds and local decision making which enable them to more efficiently and effectively conduct their biomedical research programs.

This basic objective of the Biomedical Research Support Grant (BRSG), as established by legislative history and intent, is to extend opportunity and responsibility to the scientific/administrative leadership at the institutional level for making specific on-site allocations for biomedical research purposes. This is to assure that a portion of the total NIH funds for biomedical research utilizes local decision making, allowing for appropriate internal balancing of needs as well as early recognition and development of emergent research concepts, techniques and talent.

Program Activities:

- REVISION OF THE REPORTING REQUIREMENTS FOR GRANTEES

In keeping with the Administration's commitment to reduce the reporting burden on academic and scientific institutions the format for the BRSG Annual Progress Report was revised for the reporting period April 1, 1980 through March 31, 1981. A number of specific criticisms and suggestions conveyed to us by the grantee community during the previous reporting period were considered in making the revisions. For example, five tables of program specific data were formerly required. In the revised format, only two tables of information on program specific activities are required. Instructions for preparation of the report have been made clearer and adjusted to reflect the deletion of three tables. Information requested in the narrative description section has also been reduced. It is no longer necessary to describe all major research accomplishments during the reporting period. Rather, the institutions are encouraged to describe only one or two outstanding examples of research activities supported with BRSG funds.

Grantee institution response to date has been favorable regarding changes in the format and the reduced reporting burden. Staff analyses of 1981 progress reports now underway will seek to identify other appropriate adjustments for the future.

In Fiscal Year 1980, information supplied by BRSG awardees in their annual progress reports was captured by the DRR Scientific Classification System. It was used in over 25 different reports requested by Congress and other Federal agencies regarding DRR support for a wide variety of scientific

activities including heart, lung and blood research, toxicology research, population research, prevention research, and vision research.

- REVISION OF THE BRSG COMPUTATION FORMULA

The following formula was used from 1976 to 1981 to determine the amount of the BRSG made to eligible institutions:

15% of 1st $500,000 of "allowable" research grants base
plus
10% of $500,000 to $2 million
plus
5% of $2 million to $6 million
plus
0% above $6 million

The formula applied to fixed increments of research grants activity the "allowable research grants base), had a cap at $6 million, and a 6:1 "pay out" advantage to the "smaller" institutions as measured by their level of PHS research grants activity (see Table below).

COMPARISON OF BRSG COMPUTATION FORMULA "PAY OUTS"

Type of Institutions	Formula "Pay Out" (cents award/100 cents eligible grants)		
	Current Formula		Revised Formula Based on
	The 1976 Awards	The 1981 Awards	The 1981 Awards
With least NIH research activity	9.2¢	6.3¢	4.88¢
With most NIH research activity	1.5¢	0.5¢	0.76¢
"Pay Out" Advantage	6.3:1	12.5:1	6.4:1

Since 1976 there has been a disproportional decline in size of BRSG awards to institutions most actively engaged in biomedical research. The static 1976 formula did not adjust for increases in the dollar volume of grants and the number of eligible institutions. In 1981, $596 million of the total research grants base exceeded the $6 million cap; a three-fold increase over 1976. Thus 33% of the total research grants base was not used in the computation of the 1981 awards. This caused an unintentional shift in the distribution of BRSG funds, and had the greatest impact on institutions most actively engaged in biomedical research, since the "pay out" advantage for the "smaller" institutions increased from 6:1 to 12:1.

A revised formula was developed in 1981 in concert with DRR program advisory groups which will be implemented in a 2-step fashion with the first change occurring with Fiscal Year 1982 awards (start date April 1, 1982) and the

final step with Fiscal Year 1983 awards (start date April 1, 1983). The new formula removes the $6 million cap; has self-adjusting features to compensate for changes in dollar volume of eligible grants and number of grantees; and returns to the 1976 "pay out" level of 6:1 for the "smaller" institutions.

Using this two-step procedure the BRSG computation formulae for FY 1982 and 1983 will be as follows:

FY 1982 FORMULA COMPUTATION

I	15% of 1st $500,000 of research grants base	= $_____
	plus	
II	10% of $500,000 to $2 million	= $_____
	plus	
III	6% of $2 million to $6 million	= $_____
	plus	
IV	0.6% above $6 million	= $_____

TOTAL AWARD = Sum of increments I through IV x Proration Factor[1]

[1] Proration factor =

$$\frac{\text{Total Dollars Available for the BRSG Program}}{\text{Total Dollars Computed by Formula for All BRSG Institutions}}$$

FY 1983 FORMULA COMPUTATION

I	15% of .222 x annual base factor[2]	= $_____
	plus	
II	10% of Increment I to .886 x annual base factor	= $_____
	plus	
III	6% of Increment II to 2.658 x annual base factor	= $_____
	plus	
IV	.6% of All dollars exceeding Increment III	= $_____

TOTAL AWARD = Sum of Increments I through IV x Proration Factor[3]

[2] Annual base factor =

$$\frac{\text{Research Grants Base (Total "Allowable" Dollars) for all BRSG Institutions}}{\text{Total Number of Eligible Institutions}}$$

[3] Proration factor =

$$\frac{\text{Total Dollars Available for the BRSG Program}}{\text{Total Dollars Computed by Formula for All BRSG Institutions}}$$

Using 1981 data as an example only, the approximate dollar ranges for the Increments I through IV for the FY 1983 formula would be as follows:

Increment				
	I	0	to	$750,000
	II	750,001	to	$3,000,000
	III	3,000,001	to	$9,000,000
	IV	9,000,001	to	35,000,000

These increment ranges are only shown as examples based on 1981 data and will not be those used in FY 1983.

The impact of these changes in the BRSG computation formula, on the size of awards made to various types of grantee institutions, using 1981 data as a guide, and assuming no change in the BRSG appropriation level and number of eligible institutions would be as follows:

Revised Formula Impact On:

Dollar Increases and Decreases of Award Sizes by Types of Institutions
(as applied to 1981 data)

Types of Institutions	Decreases		Increases	
	No.	Dollar Range	No.	Dollar Range
Medical Colleges	74	$3,123 to $16,109	45	$4,277 to $99,789
Other Health Prof.	89	$12 to $15,264	1	$46,306
Other Academic	150	$2,902 to $17,201	17	$1,506 to $74,270
Hospitals	57	$3,457 to $16,637	5	$41,068 to $63,014
Res. Organizations	82	$3,046 to $16,040	5	$6,870 to $65,135

Shift in Distribution of Funds as Percentage of Total BRSG Appropriation
(as applied to 1981 data)

Types of Institutions	Current Formula % Appro.	Revised Formula % Appro.	Difference % Appro.
Medical Colleges	36.0	40.2	+ 4.2
Other Health Prof.	10.4	9.1	- 1.3
Other Academic	30.1	28.7	- 1.4
Hospitals	10.3	9.9	- 0.4
Res. Organizations	12.8	11.9	- 0.9

- INITIATION OF THE BIOMEDICAL RESEARCH SUPPORT SHARED INSTRUMENTATION GRANT PROGRAM.

Planning discussions and budget projections initiated several years ago culminated in January 1981 with the inclusion of $3.7 million in the Administration's FY 1982 budget request to the Congress in January 1981 for the initiation of a competitive biomedical shared instrumentation program.

The program is being established in recognition of the long-standing need in the biomedical research community to cope with rapid technological advances in instrumentation and the rapid rate of obsolescence of existing equipment. The objective of the program is to make available, to institutions with a high concentration of NIH extramural research awards, research instruments which can only be justified on a shared use basis and for which meritorious research projects are described.

The Program was announced in the NIH Guide for Grants and Contracts, Vol. 10, No. 8, June 26, 1981. The deadline for receipt of applications was October 15, 1981. Applications will be reviewed by specially convened initial review groups of the Division of Research Grants in January and February 1982. Final program advisory will be conducted by the National Research Resources Advisory Council in June, 1982, with awards to be made in July 1982.

Eligibility:

in FY 1982, limited to the 527 institutions which received a BRS grant award in FY 1981.

only one application for a single instrument can be submitted by an eligible institution per annual review cycle.

in contrast to NIGMS Shared Instrumentation Program (meant primarily for NIGMS grantees), the BRS program is intended for a broader community of NIH supported investigators.

Awards:

for direct costs of acquisition of new, or updating of existing instruments.

limited to instruments that cost, at least, $75,000. No upper limit but maximum award is $250,000. Provisions for co-funding.

maintenance, support personnel and service costs are not allowable.

predict funding a minimum of 14 and maximum of 49 awards in 1982.

Conditions:

it is expected that the BRS Program Director and the extant BRS advisory apparatus, augmented with members with appropriate technical and scientific expertise, will be responsible for developing an application, arranging for financing, for placing and for maintaining instrument in operational order and for taking full responsibility for establishing sharing arrangements and monitoring the maintenance and usage of the instrument.

major user group of three or more NIH supported investigators who will use equipment at least 75 percent of the total usage.

minor user group may use the instrument up to 25 percent of the total, these users need not be NIH grantees but priority should be given to NIH supported scientists or to users engaged in health-related biomedical research.

- INITIATION OF AN EVALUATION OF THE BIOMEDICAL RESEARCH SUPPORT GRANT

In December 1980, the General Accounting Office issued a letter report to the Assistant Secretary of Health, Department of Health and Human Services which stated in part --

> "During our survey of the National Institutes of Health's (NIH's) Biomedical Research Support Grant (BRSG) Program, we noted that NIH did not have measurable objectives or a methodology for evaluating the program's effectiveness." and "...the BRSG objectives, as currently established, appear too general to permit NIH to effectively measure the extent to which they are met."

In addition, the Department of Health and Human Services now requires an annual submission of an evaluation plan from each of its constituent agencies.

Thus, the combined force of the GAO and Department's activities has led to a determination that another evaluation of the BRSG Program will be necessary. The last such evaluation was the 1968-1969 Roth-Boyton Report, "The General Research Support Grant Program: Its Objectives and How They are Being Met." The Division of Research Resources has submitted to the NIH a five phase evaluation plan for the Biomedical Research Support Grant Program for FY 1981 and FY 1982.

Phase One - Develop agreed-upon objectives and indicators

Phase Two - Prepare program performance summaries

Phase Three - Prepare design options for full-scale long-term evaluation

Phase Four - Prepare a full-scale evaluation design plan

Phase Five - Implementation

- INITIATION OF A STUDY OF THE BRSG ELIGIBILITY THRESHOLD AND ALLOWABLE TYPES OF GRANTS WHICH MAKE UP THE RESEARCH GRANTS BASE

The eligibility criteria for an institution to receive a BRSG of having at least three allowable PHS research grants totaling $200,000 were established in 1976. In the ensuing five year period the cost of research has increased, the total research grants base "allowable" grants used to compute the size of BRSG award has increased, and the funds appropriated for the BRSG Program have remained stable. The combined effects of these changes have been to reduce the size of BRSG awards to all BRSG grantees, and to raise serious questions about the need to revise BRSG eligibility criteria in relationship to the following issues:

1. Does meeting the current eligibility threshold imply the same level of engagement in health-related research by the grantee institutions as it did in 1976?

2. What is the minimum BRSG award which has a meaningful impact upon the research needs of BRS grantees?

Background:

In 1976, $42.8 million was awarded for the BRSG Program, and in 1981 $44.6 million was awarded; a current dollar increase of 4.2% and a constant dollar decrease of 31%.

In the period of 1976 - 1981:

The number of institutions eligible for BRS grants has grown from 441 to 527, an increase of 19.5%.

The total Research Grant Base (RGB) of BRS grantees had grown from $995 million to $1,785 million, an increase of 79%.

The average institutions' RGB has grown from $2.3 million to $3.4 million, an increase of 48%.

The average R01 has grown from $58,000 to $92,000, an increase of 59%.

The minimum BRSG award has decreased from $17,418 to $12,668, a current dollar decrease of 27%, and constant dollar decrease of 52%.

The mean BRSG award has decreased from $96,954 to $84,584, a current dollar decrease of 13%, and a constant dollar decrease of 42%.

The maximum BRSG award has decreased from $261,305 to $178,699, a current dollar decrease of 32%, and a constant dollar decrease of 55%.

In 1981:

To match growth in average R01 the BRSG award size parameters would now be: minimum $27,520, mean $153,187, maximum $412,862.

Adjustment of the BRSG eligibility threshold to match other changes would result in a FY 1981 threshold of between $300,000 and $450,000.

To match the increase in the average institution's research grants base, the threshold would have to be $300,000.

To match the increase in the average R01, the threshold would have to be $316,000.

To produce a $25,000 minimum BRSG award, the threshold would have to be $400,000.

To meet former NIH Director Shannon's 1968 recommendation to the Assistant Secretary of Health, DHEW (0.025% of total NIH research project to maintain status quo with level of engagement in biomedical research), the threshold would have to be $437,000.

By 1983:

To match growth in average R01 (1983 estimate $105,331, based on 1981 + 7% 1982 + 7% 1983) the BRSG award size parameters would have to be: minimum $31,561, mean $175,680, maximum $473,484.

Adjustment of the BRSG eligibility threshold to match other possible changes would result in an FY 1983 threshold of between $362,000 and $615,000.

To match the increase in the average R01, the threshold would have to be $362,000.

To produce a $30,000 minimum BRSG award, the threshold would have to be $615,000.

To meet former NIH Director Shannon's 1968 recommendation to the Assistant of Health, DHEW (0.025% of total NIH research projects), the threshold would have to be $522,000.

To meet a level of five times the average R01 (an implied value in the Shannon report), the threshold would have to be $525,000.

Allowable Types of Grants Which Make Up the Research Grants Base:

Currently 21 types of research grants are used to determine the research grants base of eligible institutions. Some of those grant types (e.g. P01's, P50's, and P60's) may have resource components similar to those supported by BRSG. In addition, ADAMHA research grants, which are PHS but not NIH support, are allowable toward eligibility. As a part of an examination of the eligibility issue, the question of allowable grant types warrants analysis.

The BRSG program staff intends to focus upon the problems of an appropriate eligibility threshold and types of research grants which make up the BRS Research Grants Base. An analysis of these issues will be conducted and presented to the BRS Subcommittee, General Research Support Review Committee, and the National Advisory Research Resources Council for consideration, prior to making recommmendations to the Director, NIH.

It is anticipated that such considerations and recommendations would be completed in time for implementing any changes by the time of Fiscal Year 1983 BRSG award, i.e. April 1, 1983.

- BRSG BUDGETARY POLICY ISSUE

The current national debate within and between the Executive and Congressional Branches of the Federal Government regarding budgetary policy

as it relates to allocation and redistribution of funds among the many public constituencies has raised at least two major general issues. These are the level of funding for programs and the locus of responsibility for their execution (Federal vs local decision making). With an assumption that stark economic reality will dictate a no growth or slow growth policy for many programs of the National Institutes of Health, the question arises within the context of future NIH appropriations as to --

> What should be an appropriate balance for NIH extramural funding between categorical grants and general research support for the mid-1980's?

The Biomedical Research Support Program provides flexible funds which allow the institutions to interpret their most pressing health-related research needs at any given time and to act at the most opportune time and in the most effective way to meet those needs, using funds which are immediately available at the institution. Decisions are made by an advisory group of scientists and administrators working with the institutional program director. BRS assures that a portion of the total NIH support for biomedical research benefits from local insight into institutional research needs and early recognition of emergent research concepts, techniques and talent. The program was authorized by Congress in 1960 to permit the establishment of "grants-in-aid to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research..." The balance allowed for by the Congress in the 1960 legislation between categorical funding and flexible funding was a ratio of 85:15 respectively.

This ratio was approximately 92:8 in FY 1969, was approximately 97:3 by 1976, and by FY 1981 the BRSG portion of the ratio was below 2%. Clearly what constitutes an appropriate balance in types of support in an overall no growth situation raises issues that call for active and open dialogue among the populations of individuals and institutions that make up the NIH extramural community.

We have attempted to stimulate such discussions by meeting and corresponding with representatives of a number of national organizations such as the American Association of Medical Schools, Federation of American Societies for Experimental Biology, National Association of State Universities and Land Grant Colleges, American Chemical Society and the Association of Independent Research Institutes.

Readers of this Annual Report are urged to offer their views on the questions to their constituent academic and scientific society so Federal public policy makers can better sense the opinions of this public.

- BASIC DATA TABLES -- AN UPDATE

Table I

Distribution of BRSG Awards by Size

Size of BRSG Award (in thousands)	Number of Grantee Institutions		
	FY 1976	FY 1980	FY 1981
Under $30.0	74	103	101
30 - 49.9	87	89	112
50 - 99.9	116	101	115
100 - 149.9	60	102	88
150 - 199.9	48	106	111
200 - 249.9	19	--	--
250 - 299.9	37	--	--
	441	506	527

Grant Range	FY 1976	FY 1980	FY 1981
Minimum	$17,418	$13,449	$12,668
Maximum	261,305	189,787	178,699
Mean	96,955	88,271	84,584

Table II

Distribution of BRSG Awards by Type of Institution*

Type of Institution	FY 1976	FY 1980	FY 1981
Medicine	106	117	119
Dentistry	26	30	29
Osteopathy	1	1	1
Pub. Health	12	15	14
Pharmacy	13	20	27
Veterinary Medicine	10	9	12
Nursing	3	3	5
Optometry	0	2	2
Hospitals	63	61	62
Health Departments	2	2	2
Research Institutions	71	85	87
Other Academic	134	161	167
TOTAL	441	506	527

* Academic institutions exclusive of health professional school components.

- ILLUSTRATIVE USES OF BRSG FUNDS

1) Pilot Research: Pilot studies test the validity of new ideas and the feasibility of research methods to be used in a particular study, without requiring a large support staff or a lot of materials. This reduces the risk of major cost commitments to projects that might be unproductive and, at the same time, encourages the innovative research that is the bedrock of basic science.

At a mid-western medical school BRSG funds were used to initiate a study on chronically injured livers. Portal vein perfusate flow, portal pressure, and liver weight in the isolated rat liver were monitored in the uninjured and chronically injured states. Preliminary results show that the preparation being used to perfuse the liver is viable, and further studies are testing the feasibility of perfusing both the portal venous and hepatic arterial systems with perfusate containing red blood cells, which may stabilize the chronically injured preparation and allow additional studies on the chronically injured liver. The BRS-funded pilot studies have enabled the scientists to apply for and receive a five-year Clinical Investigator award from the National Heart, Lung and Blood Institutes as well as a one-year grant from the local Heart Foundation.

2) Support of New Investigators: New investigators bring new ideas and new skills that increase the quality and productivity of research. BRSG funding allows them to set up laboratories, conduct initial research and gain post-training research experience until they have established themselves as independent investigators.

At a west coast hospital a young investigator was well trained in both genetics and ophthalmology and was able to use BRSG funds to help launch his research career in academic opthalmology related specifically to children. He has now been able to transplant human cancer tumor in mice, test a new type of cancer treatment, and has undertaken a large scale study on blood samples. The BRSG award helped establish his laboratory and to compete successfully for an NIH grant. He presented his data to an international meeting and was appointed Research Fellow at the Hospital, demonstrating the local, national and international results from the initial BRSG funding.

3) Central Shared Equipment and Facilities: Several investigators may need the same instrument for their individual projects, but could not justify the entire need from any individual grant. Shared equipment minimizes the research costs by avoiding duplication and may reduce the time required to complete certain phases of a project. Overall quality of research may be enhanced through use of shared equipment to answer important questions that otherwise could not have been investigated, or it may improve the precision and reliability of findings.

BRSG funds were also used to strengthen the centrally supported amino analysis facility at a southern university because of the crucial need for amino acid analysis research service by many investigators. The model purchased reduces analysis time to a quarter of that required by the obsolete

instrument and also drastically reduces the amount of reagents used. It is expected through establishing a reasonable user fee it will become a self-supporting facility.

4) Provides Interim Funding: Continuity is important to save research projects from being interrupted or abandoned before completion. Interim funding may become critical when a project's continuation grant is approved but will not receive funding for several months. This can force professional and technical personnel into other activities, making them unavailable when project funding resumes. BRSG funding at this point keeps the staff on the project and prevents the need for costly reassembly and training of a new research team when project grant support is resumed.

At an eastern medical center BRSG funding successfully bridged a financial gap between two NIH research grant periods and extended studies on isolated and separated adrenocortical cells in vitro to the functional level. The results of the studies done during the interim period have been presented at two national meetings.

5) Complements Other Research Funding: In some instances, partial funding for a research project is available from one or more sources, and BRSG funds are used to fill in and unite the pieces into a complete research project.

The National Science Foundation funded a centralized amino acid analyzer facility, which served several institutions. Each institution provides funds for staff and supplies for the first two years of operation. One institution, utilizing the facility for health-related research, used BRSG funds for this purpose. After the initial two years, the facility will be supported by funds from a core of user scientists.

6) Improvement in Research Skills: Obtaining investigators with new skills may become necessary when a research project has to be redirected because of new research findings.

At a northeastern institution BRSG funds were used for the initial costs of securing the special skills of an expert on pulsed, high-frequency nuclear magnetic resonance spectrometry. This expert joined a team of scientists to develop a new complex instrument system that will apply highly advanced knowledge of physics to the understanding of the fundamental molecular basis of human disease.

FISCAL YEAR 1981
ANNUAL REPORT
MINORITY BIOMEDICAL SUPPORT PROGRAM
DIVISION OF RESEARCH RESOURCES

GENERAL RESPONSIBILITY

The Minority Biomedical Support (MBS) Program is charged with the responsibility of trying to rectify the problem of the underrepresentation of ethnic minorities in biomedical sciences. Resolution of this problem is approached through the granting of institutional awards focused on providing minorities equality of opportunity to engage in biomedical research. The MBS Program supports projects designed to strengthen biomedical research capabilities of institutions with a significant commitment to minorities, and to increase and expand the involvement of faculty and students in biomedical research.

SPECIFIC OBJECTIVES

The mission of the MBS Program is to increase the numbers and quality of minority biomedical scientists. This can be accomplished by developing and strengthening the biomedical research setting at minority (eligible) institutions so that the opportunities are expanded for the involvement of ethnic minority faculty and student investigators in biomedical research.

The MBS Program provides funds for released time so that faculty may have the opportunity to conduct biomedically oriented research. Equipment, supplies and necessary renovations for approved research projects are supported by this Program. Funds are also provided for student participation in research. Consortia, collaborative arrangements, special summer projects, and travel to scientific meetings are other activities supported by the program.

In June 1974, the Director of the National Institutes of Health requested that all Bureaus, Institutes and Divisions initiate and coordinate their minority program activities through the existing minority programs (i.e., Minority Access to Research Careers Program (MARC), (NIGMS), and the MBS Program, (DRR). It is through this mechanism that the Co-funding Agreements between the Institutes and the MBS Program were forged. Co-funding Agreements provide for the transfer of funds from one Institute to another for the purpose of supporting elements in the programs of the awarding unit. In this manner, the Institutes' at NIH can identify MBS subprojects that fit within the scope of their mission and funds are transferred to DRR for support of the projects through the MBS grants.

Growth and Scope of the Program

The Program awarded the first grants to 38 institutions in 1972 with a budget of $2 million. The number of grantees has increased to 82 in 1981 with an appropriation of $18.8 million.

The grantee institutions had been subsidizing the indirect costs until Fiscal Year 1979 when the Congress approved and appropriated funds for payment of indirect costs. Therefore, since 1979, the appropriation has included an additional $3-4 milion for indirect costs.

Currently, the MBS Program is serving the minority community through 3 grants that serve primarily American Indians, 47 serving primarily Blacks, four serving primarily Puerto Ricans in Puerto Rico, two in Hawaii and the remainder, serving a mixed population of minorities in the large metropolitan areas and the southwest. This year three new grants were awarded to schools in Colorado, Missouri and Tennessee.

With the initiation of a new computer program MBS is able to immediately access information on Intra-agency and Co-funding Agreements. The DRR system will ultimately interact with the IMPAC System and provide information on each subproject such as the name of the investigator, the project title and direct and indirect costs for the current and future years of support. A computer printout is periodically sent to each BID to keep them informed of ongoing and future commitments. The level of intra-agency co-funding has increased from $340,000 in 1975 when 8 subprojects were supported to $6.04 million in FY 1980 when 145 subprojects received support through other BID's. During FY 1981, a total of 156 projects were supported at a level of $6.42 million. The Environmental Health Sciences Institute has indicated interest in joining 9 other Institutes at NIH and the NIMH to co-fund some of the subprojects in MBS grants. This will expand the opportunities for MBS investigators interested in research relevant to environmental health problems.

ADMINISTRATIVE ACTIONS

Review Procedures

A new review procedure was introduced this year in order to improve the review of individual subprojects and reduce the workload of staff and committee members. Instead of conducting site visits to review a number of supplemental applications, panels, established along disciplinary lines, were set up at NIH to review various subprojects. Each subproject was reviewed separately and assigned a priority score on the basis of scientific merit. The Initial Review Group then reviewed the entire application from each applicant for its total merit and relevance to MBS goals.

A subcommittee of the IRG will review the results of this procedure and consider the more useful and applicable features of the panel procedures to be incorporated into the total review package of the program.

Program Evaluation

A plan for evaluation of the program in FY 1982 was developed during FY 1981. A draft of the plan, identifying the specific objectives and the criteria to be used as measures for evaluation, was developed at a workshop during the

annual Program Directors' Meeting. This plan developed with the help of the constituency was reviewed by the Advisory Committee and Council.

A Program Performance Summary was prepared from the plan and submitted to the Associate Director for Program Planning and Evaluation, NIH.

Policy Amendments

For the past two years the staff and reviewers have identified needs relative to policies or guidelines relative to supplemental applications and the level of support for investigators who have other sources of research support. A set of amendments to the Policy and Information Statement was developed and approved by the Advisory Committee and Council. Guidelines to applicants and reviewers concerning the appropriate release time support through the MBS Program were also discussed and agreed upon.

COLLABORATIVE ACTIVITIES WITH OTHER DRR PROGRAMS

In FY 1980, an agreement was established between the MBS Program and the Biotechnology Branch whereby MBS grantees could and did become users of the PROPHET system. The PROPHET system is a highly integrated collection of powerful computer-based tools for the organization, manipulation, analysis, and communication of research data and related information. PROPHET's capabilities are packaged in convenient, easy-to-use form and made available nationwide via a telecommunication network and remote graphic display terminals. PROPHET exists to facilitate laboratory and clinical investigations concerned with how chemical substances influence--and are influenced by--life processes. There are now PROPHET sites at five MBS institutions involving about 110 faculty and student users. The system has opened up a new world of opportunities and experiences for this group of investigators. It has also brought investigators from prestigious institutions in touch with this new pool of student investigators.

A second collaborative effort between the MBS Program and the General Clinical Research Centers Program resulted in an application from Meharry Medical College for a grant to develop clinical research capabilities of Meharry Medical School. This was approved and funded through the MBS Program with the GCRC participating through a Co-funding Agreement.

ACCOMPLISHMENTS

Student Participants

A total of 975 undergraduate students participated in the program in FY 1981. All of the Progress Reports for FY 1980 have not been received but the data available from 62 grantees shows that 499 MBS students received the B.S. degree. Their career choices after graduation led them to: medical school, 129; dental school, 24; graduate school, 137; and other health related schools, 115. This year 80% of the MBS graduates from the four junior colleges in the program transferred to four-year schools to continue their training in biomedical areas.

The graduate student participation in the program for FY 1981 numbered 368. An estimated ten of these completed the Ph.D. and 90 completed the M.S. degree. About 400 students presented papers at the Annual MBS Symposium held in Albuquerque this year. About 40 MBS students spent the summer in research participation at NIH laboratories. These students were sponsored by the Allergy and Infectious Diseases Institute, the Cancer Institute, the Heart Lung and Blood Institute, and the Neurology Institute.

Faculty Investigators

A total of 636 faculty participated in 507 projects in FY 1981. No data are available yet for FY 1981 on accomplishments, but 63 grantee reports for FY 1980 show that there was a significant amount of research accomplished. There were 305 scientific papers published and 757 presentations made at scientific meetings in 1980. Several more MBS faculty have been nominated to NIH advisory and review committees to augment or replace the 30 that were members last year.

The quality of science at MBS supported institutions and the reputations of MBS investigators have continued to increase. Examples of the research efforts are the following:

An investigator in the Department of Natural Sciences at Medgar Evers College and collaborators at the Albert Einstein College of Medicine have been the first to demonstrate that there are drug binding sites in the pedal ganglia of the marine mollusc Mytilus edulis. The nervous system of this invertebrate is considerably less complicated than mammalian systems but is a good model for monitoring cellular and electrical changes induced by drugs. The investigator chaired a session and reported on his research at the XVIII International Congress of Physiological Sciences in Budapest, Hungary in July 1980. He plans to present new research findings at the International Congress on Comparative Neuropharmacology to be held in Japan in 1981.

Investigators at Bishop College, an undergraduate institution in Dallas, have developed a rapid (four minute) procedure using ^{125}I to qualitatively and quantitatively determine the molecular weight of RNA samples. This rapid iodination procedure, when combined with two-dimensional gel electrophoresis, simplifies identification of RNA without interference from impurities.

At Howard University, an investigator is carrying out research on breast tumor growth. By studying mammary cancer induced in laboratory rats by a carcinogenic agent, he is beginning to delineate the role of hormones and certain hormone inhibitors on the rate of tumor growth. Approximately 40 percent of the mammary carcinoma occurring in American women appears to be hormone dependent. Recently, it was demonstrated in this laboratory that the compound CI-628, a female hormone antagonist, which competively binds to hormone receptors, induces tumor regression and terminates the synthesis of an important

catalyst in tumor cells. It was also shown that another female hormone antagonist, progesterone, results in a blockage of the biological processes involved in tumor development.

Anti-inflammatory steroids are being developed by researchers in the College of Pharmacy at Florida A&M University in Tallahassee. Studies in rats indicate that two new compounds have a marked local anti-inflammatory action without any of the usual toxic effects caused by the corticosteroids currently employed for topical application.

Biologists at the University of Puerto Rico, Rio Piedras campus, are developing a vaccine against schistosomiasis, a parasitic disease which affects 10 to 15 percent of Puerto Ricans and over 200 million people in tropical areas throughout the world. Tests of a new vaccine, isolated from a related parasite, Fasciola hepatica, which infects the livers of cattle and sheep, gave a significantly higher degree of protection than has been obtained using other methods. Efforts are continuing to improve the vaccine to achieve at least 80% protection consistently, to identify all the protective antigens and optimize treatment regimens and, eventually, to test the vaccine in non-human primates.

MBS investigators at the University of Maryland, Eastern Shore, have been studying marine algae in order to isolate medically active compounds (bioactive compounds from natural sources include digitalis, reserpine, atropine and colchicine). They are studying a species of marine "red-tide" dinoflagellates which produce some of the most potent toxins known to man. The study of the toxins is important not only for the potential of obtaining new compounds for the treatment of disease, but also for the development of an effective treatment for human or animal intoxication from venoms of toxic marine organisms. The team has been successful in culturing large volumes of cells under conditions which promote high toxin production, and has improved techniques for harvesting and purifying the toxic material so that physiological, pharmacological and toxicological studies can be carried out without delays due to unpredictable toxin supplies.

The Annual MBS Symposium

The symposium, held in Albuquerque, New Mexico, attracted about 1,500 participants. Among the highlights were 272 papers and 212 posters presented by student and faculty investigators. Three mini symposia were also conducted. The symposia topics were; "Endorphins: Natural Pain Killers", "The Fetal Alcohol Syndrome" and "Recent Advances in Cancer Research." A workshop on grantsmanship was also conducted by NIH staff and some members of NIH review committees.

Invited speaker U.S. Senator Harrison Schmidt talked about the experiences that led him to become a scientist astronaut who visited the moon and then turned to politics. The informative lecture given by Congressman Manuel

Lujan of New Mexico described the process by which an idea becomes a bill in Congress and how that bill is enacted into a law. The George Willis Memorial lecture featured Dr. John Baxter in a presentation, "Application of Recombinant DNA Technology".

MBS Resource Development Highlights

A 3-year grant to Howard University, College of Medicine has just been completed. This non-renewable support, limited to one three-year period, has assisted them in developing their research capability in cellular and molecular biology has been completed. They are now competing for regular research grants and are productively engaged in state-of-the-art biomedical research and research training.

A similar situation has developed at the Atlanta University Center involving a consortium of 5 institutions. These institutions, prior to the MBS Program, did not have significant biomedical research capabilities and especially did not have access to centrally-shared research resources. The MBS Program has provided the funds so that in the past year they have been able to establish a complete electron microscopy resource for transmission and scanning electron microscopy with computerized capability. They have also been able to complete their centrally-shared instrumentation resource for biochemistry and molecular biology research. This latter resource involves high resolution spectrometry of various sorts and a computer facility that includes a hookup with the PROPHET System of DRR. Completion of these resources is beginning to payoff with productivity in state-of-the-art biomedical research and research training. The scientists are now able to compete for research support with scientists at the more prestigious and established universities.

In Puerto Rico, at the Rio Piedras Campus, University of Puerto Rico, there is now a very productive laboratory of immunology established and developed by the MBS Program. The investigator is considered an authority on immunological research and his laboratory is a pioneer in immunodiagnosis, having published 21 papers on this topic in the last three years.

At Incarnate Word College, San Antonio, Texas, 148 students have participated in the MBS Program since 1973. Twenty-two have been awarded the M.D. at various medical schools; twenty-eight are presently enrolled in medical school; seven have been awarded the D.D.S.; eleven are currently enrolled in dental school; fourteen have been awarded the M.S. degree; ten are currently enrolled in graduate school (four Ph.D. candidates), and twenty-six are employed in health related fields.

OFFICE OF GRANTS AND CONTRACTS MANAGEMENT

The Office of Grants and Contracts Management (OGCM) continues to play an important role in the review, negotiation, award making, and the administration of the Division grant programs, as well as aiding in the administration of contracts that are made by the Research Contracts Branch, Division of Contracts and Grants. During FY 1981, a total of 1,090 grant awards in the amount of $173,880,000, and 20 contract modifications and 2 intra-agency agreements in the amount of $4,515,000 were made.

There were a number of revised awards that had to be made because of the uncertainty of FY 1981 funding of DRR Programs. This created an additional work load for OGCM as well as uncertainties and confusion for the grantee community. OGCM developed a new funding mechanism called "Co-Funding". Co-Funding allows the various NIH Institutes to directly co-fund an award along with the awarding Institute or Division that administers the grant. Co-Funding was used for funding the FY 1981 Minority Biomedical Support (MBS) grant program as an NIH trial for this mechanism. A total of $5,554,587 through Co-Funding was provided by the various NIH Institutes, and $923,000 was received from NIMH through an intra-agency agreement for a total of $6,477,587. OGCM conducted an educational program with the various NIH Institutes on how the Co-Funding mechanism works. It is believed that in the future it is a tool that will be used throughout NIH.

The following tables and charts reflect the total DRR grant and contract effort for FY 1981. Particular attention is invited to the chart titled "Division of Research Resources Research Grant Award in Current & Constant Dollars Fiscal Years 1971 - 1981." It should be noted that for the past two years there has been a very slight upward trend of constant dollars compared to current dollars.

DIVISION OF RESEARCH RESOURCES
FY 1981 OVERVIEW OF GRANT AND R&D CONTRACT PROGRAMS

Program	Funding	Major Resources Supported
General Clinical Research Centers Program	$ 60,148,000	• 75 General Clinical Research Centers (Includes two phase outs) • Over 3200 Research Projects • 40 Clinical Associate Physicians • 2 Contracts
Biotechnology Resources Program	$ 19,642,000 1/	• 48 Biotechnology Resources __ 17 Computer Resources (3 contracts) __ 3 Biomedical Engineering Resources __ 24 Instruments for Biological Structure and Function __ 1 Cellular and Biochemical Material Resource
Animal Resources Program	$ 25,052,000 2/	• 7 Primate Research Centers, including 220 Core Research Projects • 7 Primate Breeding Projects • 60 Animal Research and Resource Project Grants and Contracts • 8 Training Programs
Minority Biomedical Support Program	$ 25,330,000 3/	• 80 Institutions • 507 Research Projects • 636 Faculty, 975 Undergraduates, and 368 Graduate Students • 5 Prophet Sites • Minority Symposium
Biomedical Research Support Program	$ 47,146,000	• Biomedical Research Support Grants to 527 Institutions • 10,000 Pilot Research/Regular Research Projects • Central Resources • Development Awards to 19 Institutions • Minority High School Research Apprentice Awards for 1219 Students
Office of the Director	$ 1,077,000 4/	• Culture Collection and Research Resources Reporter Contracts
Total Funding	$178,395,000	

1/ Includes $ 734,000 other than DRR appropriated funds
2/ Includes 46,000 " " " " "
3/ Includes 6,478,000 " " " " "
4/ Includes 590,000 " " " " "
$ 7,848,000

OGCM FY-1981

DRR FY 1981 GRANT AND R&D CONTRACT AWARDS BY MECHANISM

(Dollars in Thousands)

PROGRAM ACTIVITY	Research Grants: Research Centers Type	No.	Amount	Research Grants: Other Research Type	No.	Amount	Training Programs Type	No.	Amount	Res. & Develop. Contracts Type	No.	Amount
General Clinical Research Centers Program.....		M01s			P09s					New		--
	2	18	$14,168	3	1	$ 200				Mod.	2	$ 40
	3	19	718									
	5	58	45,022									
		95	$59,908									
Biotechnology Resources Program.....		P41s			P09s					New		--
	1	3	$ 767	3	1	$ 84				Mod.	8	$2,651
	2	8	4,491		R01s					Intra-Agency		84
	3	11	1,882	3	1	$ 25						$2,735 1/
	5	25	8,728		R13s							
		47	$15,868	1	3	$ 42						
					R23s							
				1	1	$ 56						
					R24s							
				2	1	$ 322						
				5	2	510						
					3	$ 832						
Laboratory Animal Sciences and Primate Research Program.....		P40s			P09s			F32s		Mod.	8	$ 502
	1	5	$ 681	3	1	$ 120	1	1	$ 19	Intra-Agency		61
	2	8	1,219									$ 563
	3	6	202		R24s			T32s				
	5	27	3,726	2	2	$ 287	5	8	$ 575			
		46	$ 5,828	3	1	2						
				5	7	428						
		P51s			10	$ 717		T35s				
	2	2	$ 4,537				5	1	$ 13			
	3	2	2,814									
	5	4	9,866									
		8	$17,217 2/									

DRR FY 1981 GRANT AND R&D CONTRACT AWARDS BY MECHANISM (CONTD)

(Dollars in Thousands)

PROGRAM ACTIVITY	Research Grants: Research Centers Type	No.	Amount	Research Grants: Other Research Type	No.	Amount	Training Programs Type	No.	Amount	Res. & Develop. Contracts Type	No.	Amount
Biomedical Research Support Program.....				P09s 3	1	$ 18						
				S03s 1	230	$ 999						
				S07s 1	24	$ 768						
				2	503	43,808						
					527	$44,576						
				S08s 5	19	$ 1,553						
Minority Biomedical Support Program.....				P09s 3	1	$ 200				Mod.	1	$ 100 6/
				R13s 5	1	$ 62						
				S06s 1	3	1,230						
				2	19	6,497						
				3	9	615						
				5	57	16,626						
					88	$24,968 5/						
Office of the Director....										New Mod	2	-- $1,077 4/
TOTAL		196	$98,821		884 5/	$74,452		10	$ 607		20	$4,515

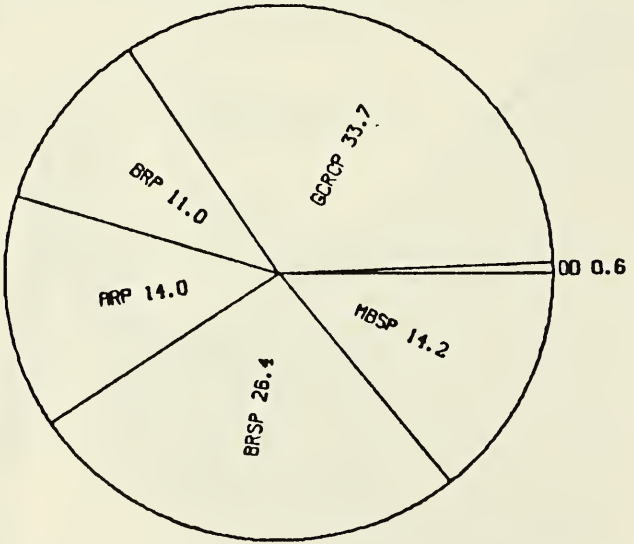
1/ Includes $ 734 other than DRR appropriated funds
2/ " 46 " " " " " "
3/ " 6,478 " " " " " "
4/ " 590 " " " " " "
$7,848

5/ Each DRR Program contributed to Scientific Evaluation Grant (P09). Counted only as one grant under the Biotechnology Branch.

6/ Used to support Prophet. Count included in Biotechnology contract number.

OGCM FY-1981

DIVISION OF RESEARCH RESOURCES
FY 81 AWARDS BY COMPONENT
Research Grants, Research Training, and R&D Contracts



OGCM FY-1981

DIVISION OF RESEARCH RESOURCES

FY 81 AWARDS BY COMPONENT

Research Grants, Research Training, and
R&D Contracts

General Clinical Research Centers Program	Research Centers	$ 59,908,000	
	Other Research	200,000	
	Contracts	40,000	
		$ 60,148,000	(33.7%)
Biotechnology Resources Program	Research Centers	$ 15,868,000	
	Other Research	1,039,000	
	Contracts	2,735,000	
		$ 19,642,000	(11.0%)
Animal Resources Program	Research Centers	$ 23,045,000 1/	
	Other Research	837,000	
	Training	607,000	
	Contracts	563,000	
		$ 25,052,000	(14.1%)
Minority Biomedical Support Program	Other Research	$ 25,216,000	
	Contracts	100,000	
		$ 25,330,000	(14.2%)
Biomedical Research Support Program	Other Research	$ 47,146,000	(26.4%)
Office of the Director	Contracts	$ 1,077,000	(.6%)
		$178,395,000	(100%)

1/ $17,217,000 of this amount was for Primate Centers.

DIVISION OF RESEARCH RESOURCES
Research Grant Award in Current & Constant Dollars
FISCAL YEARS 1971 – 1981



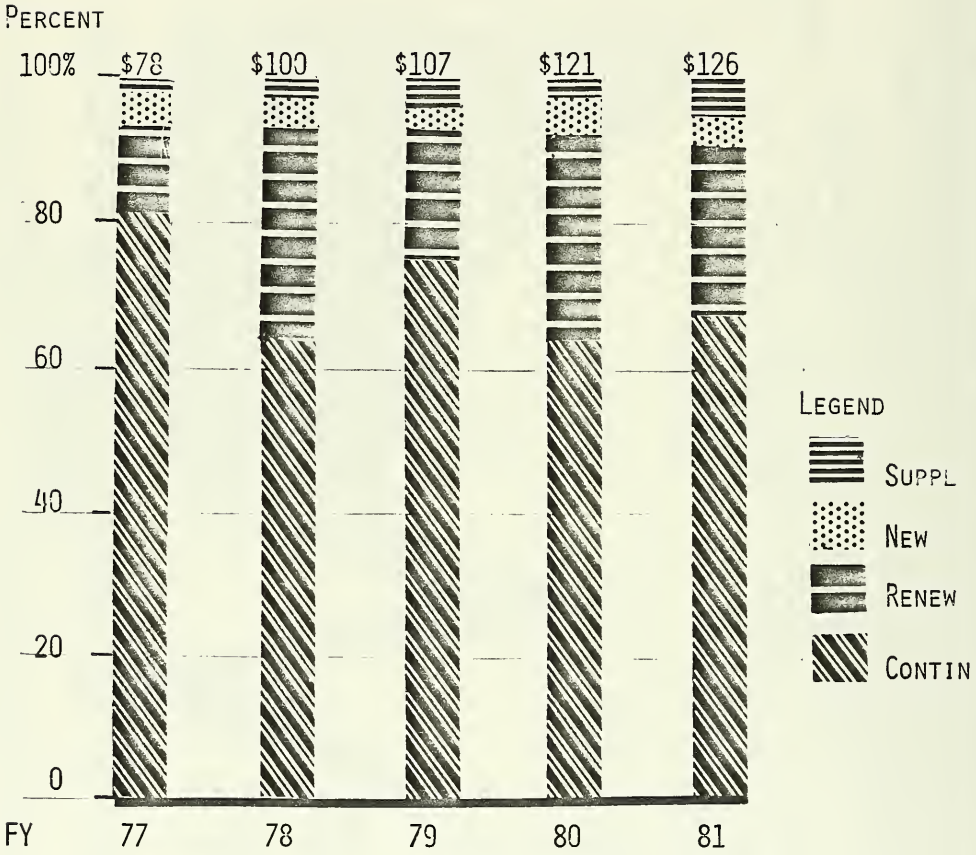
NOTE: CONSTANT DOLLARS BASED ON BIOMEDICAL R&D PRICE DEFLECTOR FY 1971 = 100

OGCM FY-1981

SOURCE: BASIC DATA BOOKS FY 71-81, NIH, PHS, DHHS

DRR RESEARCH GRANTS BY TYPE
FISCAL YEARS 1977-1981

(PERCENT OF AMOUNT AWARDED; DOLLARS IN MILLIONS)

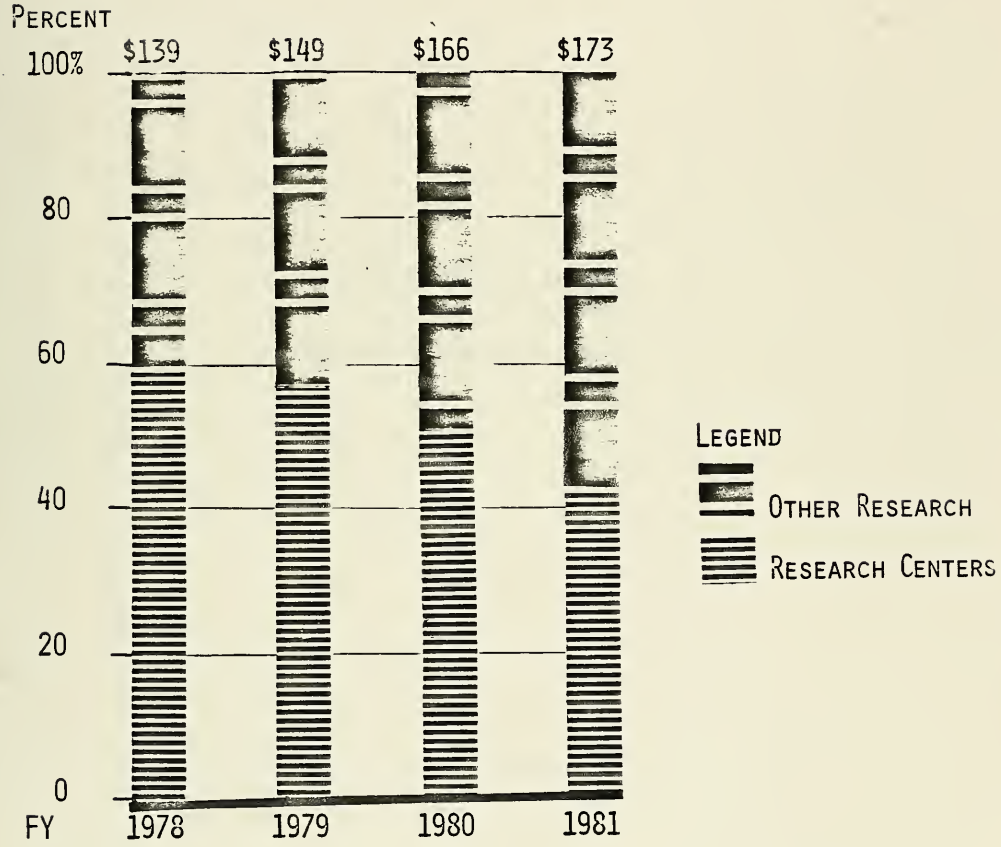


NOTE: EXCLUDES BRS AWARDS

SOURCE 77-80 DATA: NIH, DRG, STATISTICS & ANALYSIS BRANCH

DISTRIBUTION OF DRR RESEARCH CENTERS AND OTHER RESEARCH GRANTS FISCAL YEARS 1978-1981

(PERCENT OF DOLLARS AWARDED)
(IN MILLIONS)



NOTE: INCLUDES BRS PROGRAMS
EXCLUDES SCIENTIFIC EVALUATION GRANTS
SOURCE 78-80 DATA: NIH, DRG, STATISTICS & ANALYSIS BRANCH

VRB Special Project Reports

1980-81 DRS ANNUAL REPORT

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00001-11 VR

PERIOD COVERED
October 1, 1980 - September 30, 1981

TITLE OF PROJECT (80 characters or less)

Animal Model Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: C.T. Hansen Geneticist, SAS VRB, DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The development of biological test systems to meet the future requirements of biomedical research is of necessity long term and resource intensive. An integral part of the management of the National Institutes of Health Genetics Resource (NIHGR) has been the formation of new animal models and since its inception about 10 years ago, approximately 75 new models have been developed utilizing the internal resources of the NIHGR. These models which are designed to support clinical research are developed in close conjunction with the clinical investigator. Areas in which models have been or are being developed, include immunology, infectious diseases, behavior, neurology, diabetes mellitus, cardiovascular diseases to include hypertension, cerebral and myocardial infarcts and metabolic diseases.

Objectives: To develop biological test systems for a broad spectrum of biomedical research which are presently or will be needed for future studies in a broad area of clinical research.

Methods Employed: The fundamental requirement is that the characteristic of interest has a substantial genetic component. The technique followed in developing the model depends upon the manner in which the trait in question is inherited. Once this is determined, the appropriate mating scheme to develop, maintain and produce the model in question is established. Close association is maintained with the investigator during the developmental phases. The investigator has the responsibility for conducting the technical or "bench" work.

Major Findings: Due to the diverse nature of the project, it is difficult to establish any specific major findings. The most sensitive measure of the effectiveness of the program is investigator interest. In these terms, many of the models are finding increasing demand both for the NIH intramural programs as well as non-NIH programs, domestically as well as internationally which implys that the research results using these is of importance to the research community.

Significance: The program is designed to complement rather than to compete with similar efforts elsewhere. It concentrates in developing models which for a variety of reasons are not possible in other organizations. The result has been a series of models which are unique to the NIH. This in turn has provided the NIH research community with a resource which is unparalled.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00002-10 VR

PERIOD COVERED
October 1, 1980 - September 30, 1981

TITLE OF PROJECT (80 characters or less)

Development of Diets for Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.J. Knapka Nutritionist, SAS VRB, DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	0.5	2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A continuing program in laboratory animal nutrition involves various stocks and strains of rats, mice and guinea pigs as well as various species of nonhuman primates. A series of factorial designed feeding trials are used to evaluate the effect of diets made from different combinations of ingredients or those varying in nutrient concentrations on the growth, reproduction, maintenance and general health status of the species involved. The objective of this program is to improve the nutritional status of production and research animal colonies by providing diets with nutrient concentrations that are more consistent with the actual requirements. To accomplish this objective, open formula natural ingredient diets are developed. Data generated by this program are used as a basis for estimating the nutrient requirements of the species involved and also for ascertaining difference in nutrient requirements for stocks and strains within a species.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To improve the status of production and research colonies of laboratory animals by identifying the quantitative nutrient requirements of each species and providing open formula diets containing the required nutrient concentrations to identify potential differences in nutrient requirements among stocks and strains of small laboratory animals as well as different species of nonhuman primates. In addition, attempts are made to identify differences of growth, reproductive and maintenance stages of the life cycle for the species of interest. To provide NIH investigators with modifications of open formula diets to accommodate specific research projects.

Methods Employed: A series of factional designed feeding trials are conducted to ascertain the effect of varying dietary concentrations of nutrients or different feed ingredients on growth, reproduction and maintenance of small laboratory animals. Criteria of dietary evaluation include number of pregnancies, number of litters born and weaned, number of pups born and weaned, preweaning mortality, weight of offspring weaned and the post weaning growth of offspring. Diets for maintenance are evaluated by determining longevity.

Similarly designed studies are conducted involving nonhuman primates. However for these species the primary criterion for evaluating diets has been palatability or acceptability. Methods for improving diet palatability are continually being evaluated. Where practical, data from studies are coded for computer analysis by the appropriate statistical methods.

Major Findings: Open formula diets for small laboratory animal species that have been developed as a result of this program are presently being used throughout NIH and the biomedical research community. The use of these diets by institutions involved in biomedical research is expanding. Perhaps the most important contribution of these diet formulations has been the flexibility they provide for making modifications to produce special diets to meet the requirements of specific research projects. Although the cost differential between open and closed formula diets continues to be approximately 30%, a marmoset diet has been developed that has maintained a small number of animals for approximately two years showing that it is possible to develop an adequate diet for this species. However, there are still some problems associated with palatability of this diet for some marmoset species. The development of an extruded open formula diet for nonhuman primates is being accomplished and has progressed to the point where a diet is being evaluated.

Significance: The efficiency of maintaining production and research colonies of laboratory animals can be markedly improved when diets supply nutrient concentrations equal to the actual requirements of the animal species involved. Diets formulated to accomodate specific research projects, or standard diets, provide NIH investigators and the scientific community with an essential research tool when experimental data are to be verified by replicating experiments. The use of open formula diets for large animal colonies also results in a considerable economic advantage colony maintenance.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00004-20

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Tyzzer's Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.R. Ganaway	Chief, Microbiology Unit, CPS	VRB DRS
OTHER:	T.H. Spencer	Microbiologist, CPS	VRB DRS
	A.M. Allen	Chief, VPS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.3	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The continuing purpose of this project is the study of Tyzzer's Disease. The topics of present interest are: (1) characterization of the causative agent, Bacillus piliformis of which we presently have isolants from five animal species (rabbit, horse, rat, gerbil and mouse) in pure culture; (2) the serological response of the host to B. piliformis infection and the serological relationship between isolants from different animal species using the complement fixation test and fluorescent antibody techniques; (3) the pathogenesis of Tyzzer's disease in various animal species; and (4) the epidemiology of Tyzzer's disease, the goal being to identify primary sources of the infection.

PHS-6040
(Rev. 2-81)

Objectives: To characterize the etiologic agent, B. piliformis; to study the pathogenesis, the immune response and mechanisms, and to develop means to prevent or control the disease.

Methods Employed: Microbiology, immunology and pathology.

Major Findings: To overcome the costly, tedious, and time-consuming procedure of propagating B. piliformis in the yolk sac of embryonated hen's eggs, we have attempted to adapt the agent to in vitro growth in cell cultures. Preliminary studies have met with success in primary embryonic cell cultures but not in established cell lines which would be most advantageous. There is also a great need for a more objective serological test than the fluorescent antibody test which is presently used. To meet this need, we are studying the ELISA (enzyme-linked immunospecific assay) technique. Infected mouse liver suspension substrate can be used as antigen but is hazardous unless prepared in germ-free mice due to the possibility of contamination with latent indigenous agents. Unfortunately, the primary embryonic uninoculated cell culture antigen (mentioned above) binds normal (control) serum (nonspecifically) for, as yet, unknown reason.

Significance: Often occurring as an epizootic, Tyzzer's disease causes fatal disease in mice, rats, hamsters, gerbils, laboratory rabbits, guinea pigs, nonhuman primates, cats, dogs, horses, wild hares, cottontail rabbits, coyotes, and muskrats. The etiologic agent, a Gram-negative, spore-forming obligate intracellular parasite, is unique in the field of microbiology and remains unclassified. The disease occurs throughout the world and is one of the more important disease of laboratory animals that interferes with and complicates biomedical research.

Proposed Course: Continuation.

Publications:

GANAWAY, J.R. Effect of heat and selected chemical disinfectants upon infectivity of spores of Bacillus piliformis (Tyzzer's disease). Lab. Anim. Sci. 30:192-196, 1980

WAGGIE, K.S., HANSEN, C.T., GANAWAY, J.R. and SPENCER, T.H. A study of mouse strain susceptibility to Bacillus piliformis (Tyzzer's disease): The association of B-cell function and resistance. Lab. Anim. Sci. 31:139-142, 1981

GANAWAY, J.R. and ALLEN, A.M. Diagnostic Exercise: Tyzzer's disease. Lab. Anim. Sci. 31:249-250, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00011-07 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Effect of Season on Pituitary and Gonodal Hormone Levels in Adult Male Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.K. Johnson	Chief, VMSS	VRB DRS
	G.D. Hodgen	Chief, ES	RRB NICHHD

COOPERATING UNITS (if any)
Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources ranch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.25	.25	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this study is to assess the seasonal changes in endocrine parameters important in male fertility. Measurements of androgens measured as a biorhythm will be correlated to breeding efficiency and season.

PHS-6040
(Rev. 2-81)

Objectives: In most studies of infertility, the major emphasis of investigation is on the female. This study encompasses a longitudinal investigative cyclic patterns of spermatogenesis.

Methods Employed: Ten male breeder monkeys were bled the first five days of each month for a 12-month period. Follicle-stimulation hormone, luteinizing hormone, testosterone, and androsterone were assayed using sensitive radioimmunoassay methods. The results were correlated with time of month, season, and breeding efficiency. Repeated blood samples were taken to verify accuracy of radioisotope analyses of frozen serum.

Significance: Fertility and sterility studies focusing on male endocrine parameters have not been extensive. Approaching male endocrine changes as a biorhythm may lead to basic understanding of reproductive endocrinology. In addition, our results may be applied directly to biomedical research to improve nonhuman primate breeding, which is important because large-scale domestic colonies are a major resource to the scientific community.

Proposed Course: This study is finished. The results will be incorporated as baseline data for future research purposes.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 RS 00027-04 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Linkage Analysis in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit, CPS	VRB DRS
	J. S. Crowell, Jr.	Staff Fellow, CPS	VRB DRS
	K. P. Smith	Geneticist, CPS	VRB DRS
OTHER:	A. H. Grier	Biologist, CPS	VRB DRS

COOPERATING UNITS (if any)

Cell Surface Antigen Laboratory, Memorial Sloan-Kettering Cancer Center, New York, New York; NIAID; and University of Melbourne, Australia.

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory mouse inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunological techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal models of pathogenesis.

PHS-6040
(Rev. 2-81)

Objectives: To identify and locate on the chromosomes of the laboratory mouse genetic traits which can be used in a wide range of biomedical research areas.

Methods Employed: Analysis of proteins and enzymes by starch-gel electrophoresis complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic and immunofluorescence methods.

Significance: Determination of the chromosome location of these inheritable markers would permit their use in the quality control program initiated by the Genetic Monitoring Laboratory. In addition, these findings are of interest to the biomedical community with regards to the genetic characteristics of normal and diseased status.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00029-04 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Clinical Pathology Studies of Animal Health Conditions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. J. Baas	Chief, CU, ACS	VRB DRS
Other:	F. J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies are being conducted to define and characterize spontaneous diseases occurring in the NIH canine colonies. Preliminary clinical investigation has identified some disease problems. Hematological and chemical tests are being performed. The purpose of these investigations is to improve the quality of animals and animal products provided for research and characterize models of disease.

PHS-6040
(Rev. 2-81)

Objective: The objectives are to identify causes of diseases in NIH dog colonies, help determine the pathogenesis, improve the quality of animals and animal products provided, and characterize models of disease.

Methods Employed: Several standard hematological, and chemical procedures are being employed at the Animal Center and through commercial laboratories. When an unusual technique or information is needed, assistance is enlisted from various institutions.

An evaluation of methods and biologicals to prevent, control, and treat parvovirus infection in the dog breeding colonies is underway.

Major Findings: The findings in anemic blood donor dogs indicate that iron deficiency is important in some dogs but vitamin deficiencies may have major contributory roles. Biological products and hyperimmune serum evaluated thus far have been only moderately effective in preventing the disease caused by parvovirus.

Significance: It is necessary to identify the disease problems and control or eliminate them to provide improved animals and products for biomedical research. Complete characterization of some conditions may provide models of human conditions or help illustrate the pathogenesis of animal diseases.

Proposed Course: Indefinite/continuing

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00030-04 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Evaluation of Mycobacterium paratuberculosis Bacteria in the Goat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.L. Morin	Chief, PRU, VMSS	VRB DRS
	L.D. Stuart	Chief, UU, ACS	VRB DRS
	R. Merkal	Research Veterinarian	NADL

COOPERATING UNITS (if any)
National Animal Disease Laboratory, Agriculture Research Services, Ames, Iowa

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.01	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is designed to determine if a bacterin against Johne's disease will affect the incidence and age of onset of the disease in goats. One-half of the kid goats produced by Animal Center Section conventional does will be vaccinated at one month of age and observed for life.

PHS-6040
(Rev. 2-81)

Objectives: The objective is to determine if a bacterin against Johne's disease will affect the incidence and age of onset of the disease in goats.

Methods Employed: One-half of the kid goats produced by Animal Center Section conventional does will be vaccinated at one month of age with a whole-cell bacterin against Mycobacterium paratuberculosis. The other half (in most cases the twin) will be used as a control. The animals will be housed on contaminated pastures and will serve NIH programs as usual. Animal cultures will be prepared to check for M. paratuberculosis. At the end of their usefulness or when they develop clinical Johne's disease, the goats will be necropsied and their Johne's disease status evaluated.

Major Findings: Findings will not be known until 1982.

Significance: With the use of a bacterin it may be possible to prevent or delay the onset of Johne's disease in goats as it is in cattle, thus enhancing the usefulness of goats in research.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 00033-04 VR

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Application of Automatic Data Processing to Nonhuman Primate Colony Management

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. M. Renquist	Chief, PQU, ACS	VRB DRS
Others:	R. Van Wey, Jr.	MAO	OD DRS
	P. Basa	Computer Programmer	DCRT
	D. Burns	MAO	OD, DRS

COOPERATING UNITS (if any)

Division of Computer Research and Technology

LAB/BRANCH

Veterinary Resources Branch

SECTION

Animal Center Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.10	.10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Systems are being developed to computerize basic information obtained from nonhuman primates during the quarantine period, and in contract breeding operations. The systems will be used to provide clinical histories, morbidity and mortality data, drug treatment effectiveness and other information on either a colony or an individual basis. The system will ultimately be able to provide investigators with a complete clinical profile on monkeys issued by PQU and an inventory tracking system on primate breeders.

PHS-6040
(Rev. 2-81)

Objectives: The objective is to computerize basic information obtained from nonhuman primates during the quarantine period and in contract breeding operations.

Methods Employed: All routine background information including daily clinical history, diagnosis, and treatment data is computer entered on forms or by CRT. After issue of the animal the form is key punched and the data is stored for computer retrieval for quarantine purposes. The CRT program or "Primus" system is utilized for contract breeders.

Major Findings: All data have been placed in a historical archive file. Quarterly morbidity and mortality reports are received by disease, treatment, and cause of death. Epidemiologic and informational surveys on drug efficacy, disease spread, and inventory management can be provided.

Significance: The system will be used to provide clinical histories, morbidity and mortality data, drug treatment effectiveness, inventory tracking, and other information on either a colony or individual basis.

Proposed Course: Terminated due to completion of system as described.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00034-04 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Reproductive Physiology of Selected Exotic Nonhuman Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. M. Renquist	Chief, PQU, ACS	VRB DRS
	Dennis Barnard	Biologist, PQU, ACS	VRB DRS
Others:	P. K. Chakraborty	Staff Physiologist, OC	VRB DRS
	D. E. Wildt	Staff Physiologist, OC	VRB DRS
	T. L. Wolfle	Staff Behavioralist, OC	VRB DRS

COOPERATING UNITS (if any)

None .

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.2	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to establish breeding systems for producing healthy Aotus, Saimiri, Saguinus, and Cercopithecus in a consistent manner for research investigators at NIH and other interested scientists. Basic reproductive parameters being studied include duration of gestation, male and female reproductive cycles, accessory sexual organ development, male-female breeding ratios, reproductive hormone serum levels, puberty changes, infant development, and minimum reproductive age.

PHS-6040
(Rev. 2-81)

Objective: *The objective of the study is to establish breeding systems for producing healthy nonhuman primates.

Methods Employed: *Data will be collected for the following parameters: a) duration of gestation, b) male and female reproductive cycles, c) development of accessory sexual organs, d) male to female breeding ratios, e) reproductive hormone serum levels, f) puberty changes, g) infant development, and h) minimum reproductive age.

Major Findings: *Weights and measurements are being performed weekly on every owl monkey born to establish indices for normal development. To date ten animals are on the study. Weights at 6 months of age are between 402 and 563 grams, approximately one-half that of the adult. Deciduous tooth eruption patterns are similar to other nonhuman primates. It has been observed that the growth rate plateaus at one year and six months of age. The anthropometric measurement correlating most closely with increasing age during this period of time is the bitrochanteric diameter.

Significance: *The reproductive information obtained from this study will aid in breeding and rearing exotic nonhuman primates in captivity.

Proposed Course: *Indefinite/continuing

*See subprojects - Z01 RS 00051-02 and
Z01 RS 00050-02 VR

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 RS 00036-04 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Genetic Profile of the NIH Inbred Mouse Strains

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit, CPS	VRB DRS
	K. P. Smith	Geneticist, CPS	VRB DRS
	J. S. Crowell, Jr.	Staff Fellow, CPS	VRB DRS
OTHER:	A. H. Grier	Biologist, CPS	VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB; DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory mouse inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal models of pathogenesis.

PHS-6040
(Rev. 2-81)

Objectives: To identify and locate on the chromosomes of the laboratory mouse inherited traits which can be used in a wide range of biomedical research.

Methods Employed: Analysis of isozymes by starch-gel electrophoresis; complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic methods.

Major Findings: Forty-five inbred strains and substrains of laboratory mice have been characterized for 39 inherited traits. These genetic markers are distributed on 15 of the 19 autosomal chromosomes.

Significance: The genetic profile will make it possible to monitor inbred mice for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use in the biomedical community. The genetic information obtained will also make these strains more useful as animal models to the biomedical community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00038-03 VR

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Linkage Analysis in the Laboratory Rat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist, CPS	VRB DRS
	H. A. Hoffman	Chief, Genetics Unit, CPS	VRB DRS
	J. S. Crowell, Jr.	Staff Fellow, CPS	VRB DRS
OTHER:	A. H. Grier	Biologist, CPS	VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB: DRS

LAB/BRANCH

Veterinary Resources Branch

SECTION

Comparative Pathology Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a chromosome map for the laboratory rat. The project is designed to identify inherited characteristics of the laboratory rat which can be used in a wide range of biochemical research. The primary areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques, (2) development of the chromosome map by standard genetic analysis; and, (3) application of the revealed knowledge of the genetic characteristics to the exploration of new animal models of pathogenesis.

Objectives: The primary objective is to identify inherited characteristics of the laboratory rat. The genetically variable traits will be used to develop a chromosome map and a genetic profile of the laboratory rat.

Methods Employed: The primary methods of analysis are: (1) isozymes by starch-gel electrophoresis; (2) complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and (3) cell surface alloantigens by cytotoxic methods.

Major Findings: A new polymorphism was found for peptidase and the strain profiles were determined for all 26 inbred strains. Special matings were set up for the production of F_1 hybrids and backcrosses for the genetic analysis of the linkage data. The isozyme pattern for the F_1 hybrid exhibited the expected F_1 phenotypic pattern. The analysis of the backcross data indicated that the peptidase locus is not linked to any of the five previously mapped loci c, p, Hbb, Es-1, and Es-4.

Significance: The development of a chromosome map is much like putting together a jigsaw puzzle, the more traits which are already mapped the easier it is to map other traits. The linkage information from the backcross data presently being collected will make it possible to locate peptidase on the chromosome map. Once the location is determined it will make it easier to map other traits. Traits for which the genetic linkage is determined may also be used in the development of congenic strains.

Proposed Course: Continuation. Manuscript in progress.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00039-03 VR

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Genetic Profile of the NIH Inbred Laboratory Rat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist, CPS	VRB DRS
	H. A. Hoffman	Chief, Genetics Unit, CPS	VRB DRS
	J. S. Crowell, Jr.	Staff Fellow, CPS	VRB DRS
OTHER:	A. H. Grier	Biologist, CPS	VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB: DRS

LAB/BRANCH

Veterinary Resources Branch

SECTION

Comparative Pathology Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a genetic profile for the laboratory rat. The project is designed to identify inherited characteristics of the laboratory rat which can be used in a wide range of biochemical research. The primary areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) development of the chromosome map by standard genetic analysis; and (3) application of the revealed knowledge of the genetic characteristics to the exploration of new animal models of pathogenesis.

PHS-6040
(Rev. 2-81)

Objectives: The primary objective is to identify inherited characteristics of the laboratory rat. The genetically variable traits will be used to develop a chromosome map and a genetic profile of the laboratory rat.

Methods Employed: The primary methods of analysis are: (1) isozymes by starch-gel electrophoresis; (2) complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and (3) cell surface alloantigens by cytotoxic methods.

Major Findings: Twenty-four inbred strains and substrains have been characterize for ten inherited traits. A new polymorphism was found for peptidase and the strain profiles were determined. Strain profiles were obtained for three other traits which showed genetic variation. Genetic variation was not found among the remaining six traits which were analyzed. Three additional loci have been found during this year as having genetic variation among the strains. Two of these are esterases and one is a seminal vesicle protein.

Significance: The genetic profiles will make it possible to monitor the inbred rat strains for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use throughout the biomedical community. The genetic information obtained will also make these strains more useful animal models to the biomedical community.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00040-03 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Genetic Profile of the NIH Inbred Guinea Pig Strains

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit, CPS	VRB DRS
	K. P. Smith	Geneticist, CPS	VRB DRS
	J. S. Crowell, Jr.	Staff Fellow, CPS	VRB DRS
OTHER:	A. H. Grier	Biologist, CPS	VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB; DRS; and Frederick Cancer Research Center - NCI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.1	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory guinea pig inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal models of pathogenesis.

Objectives: To identify and locate on the chromosomes of the laboratory guinea pig inherited traits which can be used in a wide range of biomedical research.

Methods Employed: Analysis of isozymes by starch-gel electrophoresis; complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic methods.

Major Findings: Strain 2 and strain 13 inbred guinea pigs can be differentiated by three genetic markers; Tissue hexose phosphatase, erythrocyte catalase, and and alpha-globular serum protein.

Significance: The genetic profile will make it possible to monitor the inbred guinea pig strains for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use in the biomedical community. The genetic information obtained will also make these strains more useful as animal models to the biomedical community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00042-03 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Development of a Standard Strain of Mice for Pertussis Vaccine Bioassays

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist, CPS	VRB DRS
	T. T. Hansen	Geneticist, SAS	VRB DRS
	C. R. Manclark	Research Microbiologist	BOB FDA

COOPERATING UNITS (if any)

Pertussis Branch; Bureau of Biologics; FDA

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a standard strain of mice to be used for pertussis vaccine bioassays. Two lines of mice have been selectively bred for their susceptibility and resistance to sensitization by the histamine sensitizing factor (HSF) of Bordetella pertussis and have been designated HSFS/N and HSFR/N. After 20 generations of selection, the ability to be sensitized by HSF in the HSFS/N line has increased to 70 percent, and in the HSFR has decreased to 0.5 percent. The two lines have been further characterized for 12 biochemical isozymes.

PHS-6040
(Rev. 2-81)

Objectives: The ideal animal model for biological assays would be a strain in which the dose-response relationship is accurately predictable within a given dose range. The objective of this project is to develop a strain of mice with predictable and stable characteristics for the control testing of pertussis vaccine and other biologics.

Methods Employed: From a base population of NIH Swiss Webster stock N:NIH (SW), two lines of mice were selectively bred for their susceptibility and resistance to sensitization by the histamine sensitizing factor (HSF) of Bordetella pertussis and were designated HSFS/N and HSFR/N respectively. Weanling mice were injected with a saline suspension containing one opacity unit of pertussis vaccine, after five days the mice were challenged with histamine diphosphate. A minimum of 12 offspring were tested in each generation from each breeding pair. Almost all deaths due to sensitization occurred within one hour of injection.

Major Findings: After 20 generations of selection, the ability to be sensitized to HSF in the HSFS/N line has increased from 31 percent in the base generation to 70 percent in generation 20, and in the HSFR/N line has decreased from 31 percent in the HSFS/N line and 22 percent in the HSFR/N line. The genetic profiles have been determined for both lines for 12 biochemical isozymes. There were phenotypic differences between the lines for two of the 12 loci tested.

All testing of the HSFS/N strain in the past has been with a standard vaccine. Preparations are now being made to use the HSFS/N strain in a testing program using unknown vaccines sent to BB for biological testing. These same vaccines will also be tested using mice from the N:NIH(s) stock which are the traditional animals used for pertussis vaccine testing. Testing of the HSFS/N strain using unknown vaccines has now been completed. This data are in the process of being analyzed. Preparations are now being made to do further testing and characterization of the HSFR/N strain.

Significance: The mice from HSFS/N strain provide the biomedical research community with an animal model which is highly sensitive to the lethal effects of histamine and is easily immunized by pertussis vaccine. The genetic profiles for the HSFS/N and HSFR/N strain indicate that each is isogenic and the profiles can be used in the future to uniquely differentiate these strains from all other strains in case of possible future genetic contamination.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00043-03 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Micromethods for Cytotoxicity Testing in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. S. Crowell, Jr. Staff Fellow, CPS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop techniques for rapidly typing the cell surface antigens expressed on lymphocytes from various strains of mice. A variety of methods using both vital dye exclusion and radioisotope release are being explored.

Objective: To develop a rapid, efficient, and accurate method for typing mouse lymphocytes.

Methods Employed: Several standard serological methods have been examined for their applicability to the routine needs of the genetic monitoring program.

Major Findings: A modification of the standard human leukocyte testing methods has been adapted for routine use. All mouse strains maintained in the NIH foundation colony have now been typed for the products of the major histocompatibility locus (H-2) as well as for a number of loci controlling the expression of several T-cell antigens. Of unusual interest are several strains developed at the NIH which appear to have a recombinant H-2 phenotype; a fact that may be a considerable interest to investigators utilizing these animals.

The use of commercially available monoclonal antibodies in this typing is being evaluated. If successful, these antibodies could provide a simple inexpensive, standardized procedure by which other laboratories could verify the authenticity of their animals.

In addition, a number of antisera with broad reactivity have been produced. These antisera appear to react predominantly with the products of the H-2 locus and may prove to be a valuable tool in routine genetic monitoring.

Significance: Successful completion of this project will permit the Genetic Monitoring Program to test a large number of mice for inheritable traits with a minimum expenditure of time and funds. Interest in this project has been expressed by a number of other laboratories concerned with quality control in large mouse colonies.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00046-03 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Evaluation of Donor Safety in Leukopheresis of Canines

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. J. Baas	Chief, CU, ACS	VRB DRS
Other:	F. J. Judge	Chief, ACS	VRB DRS
	J. E. French	Research Physiologist	DBBP BoB
	J. C. Fratatoni	Director, BPB	DBBP BoB

COOPERATING UNITS (if any)

Blood Products Branch, Division of Blood and Blood Products
Bureau of Biologics, FDA

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.2	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Leukopheresis on canine blood donors is being conducted to determine if repeated removal of lymphocytes affects the immune response. Information obtained on the maximum frequency or total number of leukopheresis donations is to be extrapolated for human donors.

Objectives: The objective is to determine if frequent removal of lymphocytes will deplete their numbers, or have a detrimental effect on the immune process of the animal and remaining lymphocytes.

Methods Employed: Foxhound blood donor dogs are being leukopheresed with a Haemonetics Model 30 Blood Processor using techniques for human donors. The lymphocytes are being separated and stimulated with mitogens to measure their ability to respond.

Major Findings: Improved methodology for dog lymphocyte collection has been developed. It has been demonstrated by several mitogen stimulation methods that the immune response is impaired by frequent lymphocyte collection.

Significance: There is a definite trend to regular and frequent leukopheresis in human medicine. The effects on specific immune responses of the long-lived T lymphocyte are poorly understood. This study with the dog model will determine if there are definite detrimental effects from frequent donation.

Proposed Course: This project is being continued to study the effects of more frequent collection of lymphocytes for shorter periods of time.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00047-03 VR

PERIOD COVERED

October 1, 1980 - September 30, 1981

TITLE OF PROJECT (80 characters or less)

Screening Laboratory Animal Diets for Chemical Contaminants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.J. KNAPKA Nutritionist, SAS VRB, DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Veterinary Resource Branch

SECTION

Small Animal Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.25	.01	.24

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A program has been established for the routine analyses of feed samples for chlorinated hydrocarbons, polychlorinated biphenyls, organo-phosphates, lead, arsenic, cadmium, mercury, nitrate and aflatoxins. Nitrosamine assays are being conducted on feed samples selected at random. The objective of this program is to document the concentrations of these potential contaminants in natural ingredient laboratory animal diets and to establish the maximal permissible concentrations that can be attained on a practical basis.

Project Descriptions:

Objectives: To collect data regarding the concentrations of potential chemical contaminants in laboratory animal diets in order to obtain a basis for establishing maximum acceptable concentrations of these contaminants in diets for laboratory animals.

Methods Employed: Manufacturers of all NIH laboratory animal diets are required to collect representative samples of each production batch of diet. These samples are mailed to an independent laboratory where they are analyzed for chlorinated hydrocarbons, polychlorinated biphenyls, organo-phosphates, lead, arsenic, cadmium, mercury, nitrate and aflatoxins under an NIH contract. In addition, diet samples are collected on a random basis in the NIH warehouse and mailed to a university laboratory for nitrosamines analysis. All assay results are mailed directly to the appropriate NIH personnel for evaluation.

Major Findings: Analyses of results indicate traces of the heavy metals were detected in all samples with lead being in the highest concentrations (.09 to .92 PPM). The chlorinated hydrocarbon heptachlor was detected most frequently (66% of the samples) while methoxychlor was found in the highest concentration (.11 PPM) but less frequently. Organophosphate concentrations were variable with dieldrin occurring in 38% of the samples but diazion (occurring in 16% of the samples) was detected at a concentration of .67 PPM in one of the samples. Polychlorinated biphenyl concentrations were below detectable limits in all samples. Results of aflatoxin assays were inconclusive because there appears to be a positive correlation between their occurrence and the interval between diet manufacture and sample assays.

Significance: In recent years various NIH investigators have expressed concern regarding the potential effect residual concentrations of dietary chemicals can have on animals involved in various kinds of research. A major issue in this regard is lack of knowledge concerning the biological effect of low concentrations of dietary chemical contaminants. This program is designed to document dietary contaminant levels so these data are available for the evaluation of experimental data.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00050-02 VR

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Reproductive-Endocrine Studies in the Laboratory Cat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.E. Wildt	Staff Reproductive Physiologist, OC	VRB DRS
	P.K. Chakraborty	Staff Encodrinologist, OC	VRB DRS
Other:	S.Y. Chan	Postdoctoral Fellow, OC	VRB DRS
	S.W.J. Seager	Head, Reproductive Physiology Unit, OC	VRB DRS
	S.J. O'Brien		LVC NCI
	E.J. Baas	Chief, Carnivore Unit, ACS	VRB DRS
	P.A. Schmidt	Research Assistant, OC	VRB DRS

COOPERATING UNITS (if any)

Laboratory of Viral Carcinogenesis, NCI

LAB/BRANCH

Veterinary Resources Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The domestic cat serves as a valuable animal model in many biomedical fields including genetic, neural, ophthalmic, and metabolic research. However, controlled laboratory breeding of feline models is often unsuccessful, which is, in part, due to a lack of information on the basic behavioral-reproductive patterns of cats maintained under laboratory conditions. The overall goal of this project is a series of comprehensive investigations concerning definition of ovarian, behavioral, and endocrine relationships in the domestic cat during prepuberty, estrus, pseudopregnancy, pregnancy, parturition, and postpartum interval. Techniques and concepts developed in the latter studies have been applied to selective breeding of various cats used in taxonomic, genetic, and evolutionary analysis of felidae animal models. In addition, recent investigations have revealed the domestic cat to demonstrate unique endocrine responses to administration of the exogenous gonadotropin, human chorionic gonadotropin, an agent used therapeutically in women and laboratory and domestic animals. Overall information obtained in this project is being applied successfully to improve reproductive efficiency and breeding management within feline breeding colonies at NIH.

PHS-6040
(Rev. 2-81)

Objectives: This project, which is composed of a series of individual studies, each with specific goals, has a single overall objective: the definitive characterization of reproductive-endocrine relationships in the female cat.

Methods: Laboratory maintained cats of various ages are assigned to specific studies on the following general project subjects: 1) onset of puberty and endocrine and ovulatory response at first estrus in young queens; 2) relationship of the number of copulatory stimuli and ovulatory-endocrine responses during estrus; 3) relationship of reproductive behavior, hormones, and ovarian activity during pseudopregnancy, pregnancy, parturition, and the postpartum interval; 4) application of baseline data to selective natural or artificial breeding of felidae animal models. Data for project subjects 1-3 are obtained by frequent monitoring of sexual behavior, ovarian observation by laparoscopy and blood collection, and subsequent radioimmunologic assay for serum concentrations of estradiol, luteinizing hormone, and progesterone.

Major Findings: Comprehensive evaluations have been completed in studies designed to characterize copulatory-ovarian-endocrine relationships during estrus and the luteal phase. A significant finding was that mating stimuli induced a pituitary luteinizing hormone (LH) response during the first two days of estrus. Copulation during the latter days of estrus, however, failed to stimulate increased serum concentrations of LH suggesting depletion of pituitary gonadotropin stores or development of a transient refractory period. Characterization of pregnancy correlates has not been completed, but preliminary results indicated random ovulations occurred during gestation. This suggested that the cat may produce a pregnancy related gonadotropic hormone similar to the mare. Most recent results have demonstrated the cat ovary during pregnancy was indeed responsive to exogenous gonadotropic therapy during estrus. The latter investigation also revealed that the hormone, human chorionic gonadotropin, when injected into pregnant cats was estrogenic, increasing serum titers of estradiol and stimulating estrous behavior.

Significance: The domestic cat is used extensively as a laboratory model and serves the public as a valuable companion species. Yet compared to other common domestic species, comparatively little precise data have been published on reproductive-endocrine relationships in the cat. These series of studies provide a comprehensive understanding of reproductive control mechanisms, thus allowing improved breeding management for the production of feline research models. More recent observations have shown that this species demonstrates unique ovulatory-endocrine patterns, particularly in response to copulation or hormonal therapy. Consequently, this species will serve as a valuable experimental animal in the study of hormonal mechanisms and functions.

Proposed Course: Continuation. Projects will concentrate on the: 1) completion of ovarian-endocrine correlates during pregnancy, parturition and the postpartum interval; 2) estrogenic effect of HCG treatment during estrus; 3) application of baseline data for continued propagation of genetic feline models.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00051-02 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Reproduction in Mutant Corriedale Sheep Used as an Animal Model for the Study of Hyperbilirubinemia (Dubin-Johnson Syndrome)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. D. Stuart	Chief, UU, ACS	VRB	DRS
	D. E. Wildt	Staff Reproductive Physiologist, OC	VRB	DRS
Other:	S. C. Kalser	Liver Diseases Program Director	DDN	NIAID
	P. K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
	J. G. Howard	Guest Worker, OC	VRB	DRS

COOPERATING UNITS (if any)

Digestive Diseases and Nutrition Program, National Institute of Arthritis, Metabolism and Digestive Diseases

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A specific genetic strain of Corriedale sheep is used as an animal model for the study of liver pathophysiology, specifically, hyperbilirubinemia (Dubin-Johnson Syndrome). This project is concerned with increasing the numbers of animals available for research by the controlled breeding of individuals which genetically transmit this character. This project is utilizing what is considered to be the only existing Corriedale sheep homozygotic for this trait. Efforts are being made to obtain both homozygous and heterozygous offspring from these highly inbred individuals. Semen is also being collected artificially from rams, diluted in various cryoprotective extenders and then freeze preserved. This will ensure that long-term availability of male gametes for artificial insemination. Overall, this project allows perpetuation of this specific gene pool and ensures availability of research animals for future investigations of Dubin-Johnson Syndrome and related metabolic disorders.

PHS-6040
(Rev. 2-81)

Objective: The objective is to successfully breed and obtain offspring from a limited number of inbred Corriedale sheep which genetically transmit hyperbilirubinemia (Dubin-Johnson Syndrome).

Methods: A total of four (three rams, one ewe) inbred Corriedale sheep homozygotic for transmitting Dubin-Johnson Syndrome have been available for use. Standard breeding and management procedures have been employed. Homozygotic males are being naturally mated with both the homozygotic female and 12 outbred ewes. The latter breedings are resulting in offspring which are heterozygotic for hyperbilirubinemia. Backcrossing or inbreeding of these animals can eventually also produce offspring homozygous for the metabolic disorder. In related efforts, semen is being collected by electroejaculation from each ram once monthly. Semen has been diluted in various cryoprotective extenders and then freeze preserved in liquid nitrogen. This will ensure the long-term availability of male gametes for artificial insemination in the event of loss of live homozygotic males.

Major Findings: During the past year the three homozygotic males for this trait were used to obtain four pregnancies in unrelated crossbred ewes, resulting in the live birth of six offspring. The latter consists of four ram and two ewe lambs, all presumably heterozygotic. The ewes will be maintained for subsequent breeding to the homozygotic ram population. The heterozygotic male offspring are currently available for investigator use. The one homozygotic ewe has been maintained continually with a ram homozygous for Dubin-Johnson Syndrome and recently has exhibited evidence of breeding activity. Two of the three males consistently produce excellent ejaculates in response to electroejaculation. Specific diluent-extenders have been identified which appear to protect this spermatozoa for long-term storage in liquid nitrogen.

Significance: Only a limited number of a specific strain of sheep now exists that genetically transmits a metabolic disorder which also occurs in man. This project attempts the controlled breeding of this small population in an effort to retain this particular gene pool and ensure the availability of research animals for future investigations.

Proposed Course: Continuation. During the forthcoming year, males homozygous for Dubin-Johnson Syndrome will be mated with 12 outbred ewes to obtain additional heterozygotic offspring. Efforts will continue to obtain a pregnancy in the remaining homozygous ewe for this trait using natural or artificial breeding methods. Semen will continue to be collected and freeze preserved from each ram once monthly.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00052-02 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Development of Embryo Collection, Freeze Preservation, and Transfer Capabilities in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. Y. W. Chan	Postdoctoral Fellow, OC	VRB	DRS
	S. W. J. Seager	Head, Reproductive Physiology Unit, OC	VRB	DRS
Other:	P. M. Schmidt	Research Assistant, OC	VRB	DRS
	E. P. Teeple	Biological Lab. Technician, OC	VRB	DRS
	P. K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
	D. E. Wildt	Staff Reproductive Physiologist, OC	VRB	DRS
	R. A. Whitney, Jr.	Chief	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Numerous specific strains of laboratory mice are utilized as research models. However, immediate research needs for certain murine genetic types varies considerably. This often results in the excessive expense of maintaining many breeding animals from a certain strain which may or may not be valuable for future investigations. One alternative is the freeze preservation of embryos, which, at a later time, can be thawed and transferred to recipient dams, thus perpetuating specific strains. In this study the techniques necessary to collect, freeze, thaw, and surgically transfer mice embryos are being developed. Such procedures will eventually be used to more economically manage and store invaluable genetic stocks to ensure availability for future research investigations.

Objective: To develop methodology to effectively collect, freeze, thaw, and successfully transfer mouse embryos.

Methods: N:NIH(s) mice are being used to develop techniques. Immature mice are superovulated with a combination of gonadotropin injections and then mated with intact males. Females are then sacrificed at specific intervals after breeding and, using a stereomicroscope, the oviducts are flushed with media and examined for embryos and stage of their morphologic development. Embryos are then cultured and used to develop successful interanimal transfer or freeze preservation procedures.

Major Findings:
1. A research colony has been established to provide embryo donors and recipients regularly for embryo collection, freezing and transplantation experiments.
2. Optimal hormonal regimen for inducing superovulation in NIH mice has been obtained.
3. Necessary chemicals and equipment have been purchased and requested for routine operations of embryo collection, freezing and transplantation.
4. Successful culture of early stage (8-celled, 16-celled) embryos to pre-implantation stage (blastocysts) has been achieved.
5. Successful embryo transfer utilizing freshly collected embryos has been obtained. The highest success rate obtained was 80% recipient females (4/5) becoming pregnant and delivering live borns and the highest number of live-born in a litter was 8.
6. Freezing procedures have been developed and efforts have been initiated to minimize the freezing damage and to test the viability of frozen embryos utilizing embryo culture and transplantation techniques.
7. Embryos have been collected from the C_3H strain mice and transferred to the NIH mice recipients, and two live births were obtained.

Significance: In recent years, laboratory research has established the possibility of collecting early embryonic tissue, freezing such material and then obtaining live off-spring following thawing and transfer of the embryos to recipient females. Such procedures would have considerable application to the maintenance and preservation of animal research models for human disease. Since numerous valuable strains exist, and, since this species is easily handled and generally prolific, the mouse would appear to be an ideal candidate for testing the practical feasibility of a large-scale embryo freezing program.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00053-02 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Characterization of the Antigenic Components Specific to the Canine and Feline Ovary

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
Other:	S. Y. Chan	Postdoctoral Fellow, OC	VRB	DRS
	D. E. Wildt	Staff Reproductive Physiologist, OC	VRB	DRS
	A. P. Stewart	Research Associate, OC	VRB	DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.5	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The antigenic components of canine and feline ovaries have not been investigated. It is of importance to characterize these components and identify any antigen that may be ovary specific. Such antigens can be a target for raising ovarian antibody and, thus, provide an immunologic method to control fertility in the unwanted pet population. Results have indicated that there is at least one ovary-specific antigen in the canine, and the antibody raised against it would specifically bind with both ovarian homogenate and isolated canine ovarian cells.

Objective: To identify and characterize the ovarian antigenic composition in the dog and the cat. To raise antibodies against such antigens and use these as a probe to investigate the immunological factors involved in the reproductive process in these two species. Such antibodies may ultimately prove useful in controlling reproduction in the unwanted pet population.

Methods Employed: Rabbits were immunized against ovarian homogenates and the antisera used to characterize antigens present in the ovaries. Double gel diffusion and immunoelectrophoresis were utilized to study the precipitin bands while binding of antibody to isolated ovarian cells was demonstrated by using the immunofluorescence technique.

Major Findings: Following purification of the antisera to remove non-specific antibodies, one antigen could be shown to be present that was specific to the canine ovary. No specific ovarian antigen has so far been detected in the cat. Limited trials with ovarian antisera have indicated that it can inhibit luteal progesterone production and induce abortion and/or fetal resorption in the domestic cat.

Significance: These studies provide a way to investigate the immunological processes involved in the reproduction of the dog and the cat. Antisera raised against specific ovarian, luteal, or uterine antigens would serve as probes to investigate the fetus-dam relationship. Such studies may eventually lead to development of suitable vaccines to control unwanted pet population.

Proposed Course: Part of the work characterizing the antigenic characters of the ovaries has been reported in a doctoral thesis submitted to Baylor College of Medicine. Two other manuscripts have been accepted for publication in the American Journal of Veterinary Research and in Theriogenology. Both of these should be published during 1981. Luteal antisera generated in the goat is being characterized by gel diffusion and immunoelectrophoresis. Physiological studies are in progress for possible application in the area of pet population control.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00055-02 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Ovulation Induction in the Anestrous Bitch

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
Other:	D. E. Wildt	Staff Reproductive Physiologist, OC	VRB	DRS
	A. P. Stewart	Research Associate, OC	VRB	DRS
	S. W. J. Seager	Head, Reproductive Physiology Unit, OC	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The duration of anestrus in the bitch is highly variable and can last from 4-12 months. It would be important to reduce this time period so as to increase reproductive potential. The present study was designed to develop an effective hormone regimen to induce estrous cyclicity before four months following the last known estrous cycle or whelping. Some of the anestrous bitches used in this study were monitored for changes in ovarian activity by laparoscopy before and after sequential treatments with estradiol, pregnant mare serum gonadotropin (PMSG), and human chorionic gonadotropin (HCG). Serum samples will be analyzed for estradiol, progesterone, and luteinizing hormone.

Objective: To determine the conditions appropriate for induction of luteolysis in the canine. This study is further designed to investigate the optimum dosage and frequency of hormonal therapy to induce follicular development, estrous behavior, ovulation, and pregnancy in the anestrous bitch.

Methods Employed: Laparoscopy is utilized to observe the ovarian and uterine morphology. Animals are treated with 100 micrograms of estradiol for three days followed by two injections of a combination of 100 i.u. of PMSG and 500 i.u. of HCG, seven days apart. Animals were bred by artificial insemination three times during the period of estrus. Blood samples were collected during induced estrous cyclicity.

Major Findings: Results obtained so far indicate that pretreatment with estradiol for three to four days can induce luteolysis and cause sanguinous discharge typical of proestrus in this species. Pretreatment with estradiol followed by treatment with a combination of PMSG and HCG always resulted in induction of estrus. A variable number of follicular development and ovulations were observed by laparoscopy in some of the bitches. One bitch out of a group of three similarly treated animals was pregnant and carried 3 pups to term.

Significance: This project investigates the efficacy of different hormonal regimens to induce estrous cyclicity during early anestrus in the bitch. Development of such a treatment can improve the reproductive efficiency of the bitch by more than 50 percent.

Proposed Course: Further work is in progress. Serum samples are being analyzed for concentrations of estradiol and progesterone. Serum LH concentrations will also be analyzed. All whelping data will be analyzed and results of different treatment regimens will be compared statistically.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 RS 00056-02 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Mandibular Analysis as a Means of Discriminating Inbred Strains of Mice and Rats.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit, CPS	VRB DRS
OTHER:	A. G. Grier	Biologist, CPS	VRB DRS
	H. Blum	Physical Scientist	LSM DCRT
	J. Mosimann	Statistician	LSM DCRT

COOPERATING UNITS (if any)

SAS; VRB; DRS/ Laboratory Statistical and Mathematical Methodology, DCRT

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project is designed to determine the ability of the mandibular analysis to discriminate between inbred strains of mice and rats maintained by the VRB. Discriminant Analysis, Canonical Correlation Analysis, and Computer Image Analysis are being used to analyse data from 20 inbred strains of

Objectives: To evaluate the mandibular analysis as a tool for genetic monitoring.

Methods Employed: Analysis of data by Statistical Package for Social Sciences computer programs and computer image analysis.

Major Findings: Base line data on 20 inbred strains of mice have been obtained. Discrimination between strains is 86 percent.

Significance: The mandible could be used as a genetic character which can be used to screen a large number of mice for genetic contamination.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 00057-01 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Hormonal Control of Estrous Cyclicity and Sexual Behavior in the Nubian Goat.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
Other:	J. C. Camp	Student Scientist, ACS	VRB	DRS
	D. E. Wildt	Staff Reproductive Physiologist, OC	VRB	DRS
	L. D. Stuart	Head, Ungulate Unit, ACS	VRB	DRS
	P. K. Howard	Student Scientist, ACS	VRB	DRS

COOPERATING UNITS (if any)

Department of Physiology, George Washington University

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.30	0.25	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The goat is an important domestic animal in many countries and is raised to produce milk, meat, and hair under adverse environmental conditions. Goats have been important in the Southwestern U.S. for similar reasons for a number of years. The Ungulate Unit at the NIH Animal Center maintains a large flock of Nubian goats primarily as donors of blood components and raising antisera. Unlike most other domestic animals the basic reproductive characteristics in the female goat remain unknown. Knowledge of collection, evaluation and cryopreservation of goat semen is also very limited. The present study characterized these reproductive parameters and correlated the serum reproductive hormones with changes in sexual behavior and ovarian morphology.

Objective: The objectives are to establish the precise relationships of sexual behavior, ovarian activity with changes in serum hormone concentrations in the Nubian goat. This would aid in determining the optimum time of artificial insemination to improve fertility in this species.

Methods: Aproned bucks were used to daily monitor sexual receptivity in the female goat. Blood samples were collected once daily or once every other day during several estrous cycle starting at the beginning of the breeding season. Serum samples were analyzed for luteinizing hormone (LH), estradiol, and progesterone by radioimmunoassay. Ovarian activity was monitored at frequent intervals by laparoscopy throughout the estrous cycle.

Major Findings: Mean durations of estrus and estrous cycle were 2.8 and 21.3 days respectively. However, a number of short estrous cycles of 6.8 days were also observed in this group of animals. Such short cycles, a large proportion of which were anovulatory, occurred primarily during the first month of the breeding season (86% of all short cycles). Variations in the characteristics of the corpus luteum were also observed. The observed mean ovulation rate was 3.1, with the right ovary being 1.6 times more active than the left.

Significance: Reproductive performance of the female goat has been investigated in depth. Variations in the cycle length were primarily concentrated during the first month of the breeding season. This indicates that for optimal conception the first estrus period should not be selected for breeding. The hormonal data and the laparoscopic observation indicate that waves of follicles develop throughout the estrous cycle, but ovulation and successful formation of corpus luteum is associated with normal estrous cycle lengths of 21 days.

Proposed Course: The project is primarily complete. One abstract has been published and one or possibly two manuscripts will be written and submitted for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 00058-01 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Behavioral, Ovarian, and Endocrine Relationships in the Pubertal Bitch

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. E. Wildt	Staff Reproductive Physiologist, OC	VRB	DRS
Other:	P. K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
	S. W. J. Seager	Head, Reproductive Physiology Unit, OC	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study was to examine the possible causes of poor reproductive performance in young bitches by examining behavioral-ovarian-endocrine correlates at the first pubertal proestrous-estrous interval. The results indicated that some, but not all bitches exhibited one or more atypical reproductive patterns at pubertal estrus and that these aberrant patterns appeared to be related to endogenous hormonal insufficiencies or irregularities. Although ovulation was detected in all dogs examined, atypical observations included lack of sexual receptivity and reduced or inconsistent patterns of circulating concentrations of estradiol, luteinizing hormone, or progesterone.

Objectives: The objective is to precisely establish and analyze the behavioral-ovarian-endocrine correlates associated with pubertal onset in the young bitch.

Methods: At the onset of first detected proestrous-estrous activity, individual animals were subjected to daily monitoring of sexual behavior, twice daily blood collection for hormone analysis, and laparoscopy at 48-hour intervals to observe ovarian activity. Serum was collected and assayed for the hormones estrone, estradiol, luteinizing hormone, and progesterone.

Major Findings: One or more atypical reproductive patterns were observed in certain bitches at pubertal estrus. The ability to display normal reproductive relationships appeared related to age, since dogs which produced normal sexual behavior and endocrine profiles tended to be older than females producing aberrant patterns. For the latter group, atypical observations included lack of sexual receptivity and reduces or inconsistent patterns of the three hormones estradiol, luteinizing hormone, or progesterone. Ovulation was confirmed in all dogs, including those which failed to demonstrate sexual receptivity. These results indicated that hormonal insufficiencies or irregularities exist in certain bitches at the pubertal estrus, and that such activity appears more characteristic of first compared to later adult estrous periods.

Significance: The linking of immature and mature biological phases of any animal species is apparently dictated by a series of complex events leading to and occurring at puberty. The precise interrelationships of these physiological parameters, however, have remained obscure, particularly in the dog. The results demonstrated that the young bitch varies considerably in its ability to display normal expected behavioral, endocrine, or ovulatory responses at pubertal estrus. One or more atypical reproductive parameters were common in some of the bitches studied and these patterns appeared to have a hormonal basis. The possibility of counteracting this aberrant pattern by the use of exogenous hormonal therapy could greatly improve reproductive efficiency in pubertal bitches. The atypical results may simply be due to incomplete developmental processes normally occurring during the ontogeny of the adult cycle. Whether this immaturity exists at the hypothalamopituitary level or the ovary remains to be ascertained.

Proposed Course: Present investigation has been completed and manuscript has been accepted for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 00059-01 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Influence of inbreeding on reproductive performance, ejaculate quality and testicular volume in the dog.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. E. Wildt	Staff Reproductive Physiologist, OC	VRB	DRS
Other:	E. J. Baas	Chief, Carnivore Unit, ACS	VRB	DRS
	P. K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
	T. L. Wolfle	Staff Animal Behaviorist, OC	VRB	DRS
	A. P. Stewart	Research Associate, OC	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The NIH Foxhound colony, which employs an outbreeding and inbreeding program, was evaluated to assess the influence of increased homozygosity on overall reproductive performance and ejaculate quality. Conception rates and total number of puppies whelped and number whelped alive were greater in outbred compared to inbred lines. Duration of gestation and number of puppies surviving from birth to weaning were no different between outbred and inbred groups. Ejaculate quality also appeared affected by genotype with outbred males producing a greater average sperm count/ejaculate and sperm count/ml of ejaculate. These results have suggested that: 1) a canine breeding program using dogs with inbreeding coefficients ranging from .125 - .558 can experience reduced reproductive performance; 2) a portion of the infertility associated with conception may be attributed to the male, since inbred studs produced lower quality ejaculates compared to outbred counterparts.

Objective: The present study examined the influence of combined sire and dam inbreeding on conception rates and number of canine offspring whelped and weaned. In addition, the effect of inbreeding on ejaculate quality and testicular volume was evaluated.

Methods Employed: A total of 14 outbred and four inbred male dogs were naturally bred to 544 outbred and 51 inbred bitches, respectively. The average coefficient of inbreeding for the inbred males and females was .264 and .304, respectively. Standard normal semen collection and microscopic analysis procedures, as well as testicular measurements, were performed in all male dogs.

Major Findings: The outbred bitches produced significantly greater mean conception rates and numbers of puppies whelped, whelped alive and weaned than the inbred group. The mean duration of gestation in inbred bitches and the number of puppies dying from whelping to weaning were similar between outbred and inbred groups. Total sperm count/ejaculate and total sperm count/ml of ejaculate were significantly greater in outbred compared to inbred dogs. Although not statistically different ejaculate volume, % motility of spermatozoa and testes volume tended to be greater in the outbred than inbred males.

Significance: Little information on the specific effects of inbreeding and the relation of seminal traits to fertility exists in the male dog. Improved genetic management of a breeding colony can result in the production of a uniform genotype for maintaining a particular breed line or a population with similar inherited physiologic and biochemical genotypes optimal for experimental use. If inbreeding or interbreeding of closely related dogs is employed to obtain these goals, an overall decline in reproductive performance can be expected. The present results would further suggest that increased homozygosity of the male dog may contribute to reduced fertility rates in the bitch through the production of poorer ejaculate quality.

Proposed Course: A manuscript is being prepared for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 00060-01 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Mousepox

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. M. Allen	Chief, CPS	VRB DRS
	J. R. Ganaway	Chief, Microbiology Unit, CPS	VRB DRS
	A. Lock	Chief, Pathology Unit, CPS	VRB DRS
	G. L. Clarke	Pathologist, CPS	VRB DRS
	R. M. Werner	Veterinarian, Office of Lab Anim Sci	NCI
OTHER:	D. E. Meggers	Biologist, CPS	VRB DRS
	T. H. Spencer	Microbiologist, CPS	VRB DRS
	J. W. Owens	Electronmicroscopist, CPS	VRB DRS
	C. R. Neely	Histologist, CPS	VRB DRS
	E. F. Lenart	Histologist, CPS	VRB DRS

COOPERATING UNITS (if any)

Office of Laboratory Animal Science, NCI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	1.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the pathology, diagnostic features, clinical manifestations, and epidemiology of mousepox caused by the 1979 NIH isolate of ectromelia virus. The specific areas of interest include 1) comparison of histopathology with that produced by other strains of virus, 2) effect of ectromelia on nude mice, 3) application of immunocytochemical methods for demonstration of viral antigen in tissues, and 4) study of the spread of the virus and clinical features of the disease in an isolated colony of experimental mice.

Objectives: To improve diagnostic capabilities, study the pathogenesis and epidemiology, and gain insight into how to prevent and eradicate mousepox.

Methods Employed: Pathology, microbiology, immunology, and epidemiology.

Major Findings: The histopathologic changes were similar to those induced by other strains of ectromelia. Exceptions were less frequent liver pathology and an unusual reticulated pattern of necrosis in the liver. A new finding was severe thymic necrosis. The easiest method to confirm the diagnosis was by electron-microscopic demonstration of the virus in tissues of acutely ill mice. Confirmation was achieved also by isolation of the virus in embryonated hens eggs, primary cultures of mouse embryo cells, and disease-free athymic and euthymic C3H/HeN-nu mice, and by demonstration of viral antigen in formalin fixed tissues by the immunoperoxidase technique. In a naturally infected mouse colony the disease was evident mainly as a result of moderately increased mortality. Clinical features such as skin lesions and conjunctivitis that are easily induced experimentally were seldom observed. In a conventional animal room equipped with open racks and cages the disease appeared to spread slowly. It was confined to several shelves on two of five racks, all belonging to one investigative group.

Significance: Mousepox is one of the more serious laboratory animal diseases in terms of interference with biomedical research. Depending on many factors including the mouse genotype, strain of virus, method of caging, population density, and amount of acquired immunity, the disease may vary from explosive devastating outbreaks to mild smoldering ones. In partially immune populations of mice the disease may occur subclinically and not be immediately recognized. It may be spread between institutions by the practice of exchanging mice and tumors by collaborating scientists.

Proposed Course: Continuation

Publications:

Allen, A.M., Clarke, G.L., Ganaway, J.R., Lock A. and Werner, R.M., et al. Pathology and Diagnosis of Mousepox. Ectromelia (mousepox) in the United States, Seminar. 1980 AALAS Meeting, Indiana, October 1980 (In Press).

Werner, R.M., Allen, A.M., Small J.D., et al. Clinical Manisfestation of mousepox in an experimental animal holding room. Ectromelia (mousepox) in the United States. Seminar. 1980 AALAS Meeting, Indianapolis, Indiana, October 1980 (In Press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00061-01 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Relationship of Sexual Behavior, Ovarian Activity, and Reproductive Hormones in a Strain of Inbred Miniature Swine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. E. Wildt	Staff Reproductive Physiologist, OC	VRB	DRS
Other:	P. K. Howard	Student Scientist, OC	VRB	DRS
	P. K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
	L. D. Stuart	Head, UU, ACS	VRB	DRS
	J. C. Camp	Student Scientist, OC	VRB	DRS

COOPERATING UNITS (if any)

Immunology Branch, Immunology Program, National Cancer Institute

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.25	0.20	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In 1972, the National Institutes of Health in collaboration with the Immunology Branch of the National Cancer Institute initiated a breeding program to develop a highly inbred strain of miniature swine. From its inception, this herd has traditionally produced an average litter size of approximately five offspring per animal, considerably less than the mean litter size of eight-12 reported for standard sized domestic pigs. Unlike their standard sized counterparts little information on behavioral-ovarian-endocrine relationships exist for the miniature pig. The present study characterized these reproductive traits and determined that gross ovarian morphology and duration of estrus and the estrous cycle were similar between the miniature pig and previous reports for standard sized animals. However the miniature pig produced fewer ovarian follicles and had a reduced ovulation rate and depressed serum concentrations of hormones when compared to standard sized animals. The data suggest that the reduced litter size detected in this particular strain of miniature pig was, at least in part, the result of a reduced ovulation rate.

Objective: The objective was to establish the precise relationship of sexual behavior, ovarian activity and serum hormones in an inbred strain of miniature pig.

Methods: Adult female miniature pigs were monitored daily for sexual behavior. Blood samples were obtained frequently throughout the estrous cycle and analyzed for estradiol-17β, progesterone, and luteinizing hormone (LH) by radioimmunoassay. Laparoscopy was performed at six day intervals throughout the cycle and ovarian morphology observed and photographed.

Major Findings: Mean durations of estrus and the estrous cycle for the miniature pig were no different from previous values reported for standard sized animals. An average (±SEM) of 9.0±0.4 ovarian follicles developed/ estrous period and 96% of the follicles showed morphologic evidence of ovulation resulting in a mean ovulation rate of 8.6±0.3 corpora lutea (CL). These follicle and CL numbers were markedly less than values earlier published for standard sized pigs. The depressed ovarian activity also appeared to affect endocrine function. Although serum levels and temporal relationships of luteinizing hormone and estradiol-17β were similar to results in standard sized animals, progesterone titers were depressed in the miniature pig which was likely a function of reduced ovulation rate.

Significance: Behavioral, ovarian and endocrine relationships for the standard sized, domestic female pig have been intensively investigated. However, due to the standard pig's disadvantages of size, temperament and genetic heterozygosity, the miniature pig often has been considered a more favorable animal model, particularly in tissue transplantation investigations. The present study has characterized ovarian morphology and assessed ovulatory function in the highly inbred NIH strain of miniature pig. Of particular interest has been the finding that small litter size in this population is related to ovarian activity, specifically ovarian follicle and/or corpora lutea numbers. Whether the limited follicle production was due to variations in quantitative gonadotropin secretion, ovarian receptor function or to adverse genetic influences affected by the high degree of inbreeding remains to be determined. Results obtained can be applied to future studies employing gonadotropin therapies to improve litter size and management efficiency, thereby increasing the incidence of successful matings and availability of this research model.

Proposed Course: Study has recently been completed. One abstract has been published and two manuscripts are being prepared for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00062-01 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Investigation of fetal adrenal gland in Callithrix jacchus

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. Levine	Pediatrician	NICHHD
	D. M. Renquist	Chief, PQU, ACS	VRB DRS
	D. Barnard	Biologist, PQU, ACS	VRB DRS

COOPERATING UNITS (if any)
Developmental Endocrinology Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.1	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Callithrix jacchus is being investigated as an animal model for the study of fetal adrenal regression, an involutional process in which there appears to be a disappearance of dehydrolpiandosterone (DHA), the major steroid secreted by the fetal adrenal gland.

Objectives: The objective is to develop the marmoset (Callithrix jacchus), an animal model in the study of fetal adrenal regression. The squirrel monkey will also be investigated.

Methods Employed: Measurements are being determined of DHA blood levels in Callithrix jacchus. DHA is the major steroid secreted by the fetal adrenal gland. Studies of adrenal gland histology are performed on the adrenal glands of postnatal infant marmosets that die naturally. Placentas are obtained by C-section and extracts used to maintain the fetal adrenal zone.

Major Findings: The Callithrix jacchus fetal adrenals do undergo an involution as evidenced by DHA levels and histologic observations.

Significance: The Callithrix jacchus fetal adrenal involution provides a model to study the comparable human phenomenon.

Proposed Course: Indefinite/continuing

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00063-01 VR

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Glucocorticoid studies in squirrel monkeys (S. sciureus)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. Chrousos	Clinical Associate	NICHHD
	D. M. Renquist	Chief, PQU, ACS	VRB DRS
	D. Barnard	Biologist, PQU, ACS	VRB DRS
Others:	D. Brandon	Biol. Tech.	NICHHD
	D. Loiraux	Chief	NICHHD
	M. Lipsett	Director	CC

COOPERATING UNITS (if any)

Developmental Endocrinology Branch, NICHHD

LAB/BRANCH

Veterinary Resources Branch

SECTION

Animal Center Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.6	.2	.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The squirrel monkey is being studied to determine its usefulness as an animal model for hypercorticolism in humans through determination of its glucocorticoid serum levels and glucocorticoid receptors and the relations of these hormones to cortisol resistance.

Objectives: The purpose of this study is to determine glucocorticoid levels, glucocorticoid receptor affinity, and the relations of these hormones to cortisol resistance in the squirrel monkey. The potential use of the animal as a model for human glucocorticoid aberrations will be evaluated.

Methods Employed: Data will be collected for 1) plasma cortisol, 2) cortisol binding globulin, 3) urinary cortisol, and 4) glucocorticoid receptors.

Major Findings: The squirrel monkey seems to have a deficiency in glucocorticoid receptor affinity with a compensatory increase in serum cortisol.

Significance: The altered sensitivity of the glucocorticoid receptor in Saimiri provides a model for the study of cortisol resistance and glucocorticoid hormone action.

Proposed Course: Indefinite/continuing

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00064-01 RS

PERIOD COVERED

October 1, 1980 - September 30, 1981

TITLE OF PROJECT (80 characters or less)

Spontaneous Enzootic Staphylococcis in Athymic (Nude) Mice

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.D. Small	Animal Disease Investigator, VRB, DRS
OTHER:	C.H. Zierdt	Microbiologist, CP, CC
	T.D. Moore	Chief, Microbiology Unit, VRB, DRS
	C.T. Hansen	Staff Geneticist, VRB, DRS

COOPERATING UNITS (if any)

Clinical Pathology, Clinical Center

LAB/BRANCH

Veterinary Resources Branch

SECTION

Small Animal Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A low but persistent rate of facial abscesses occurring in the NIH nude mouse colony (barrier maintained) has been studied. Staphylococcus aureus has been identified as the causative organism. The dominant phage type is 42E with several isolates also being lysed by phages 44A and 54. Fecal carriage and abscesses were observed in 12 strains of nude mice and the fecal carriage rate is near 100 percent. However, many nude mice are retired as breeders after 9-12 months. Fecal carriage of the same S. aureus phage types occurs in non-nude cagemates but abscesses have not been seen. Nasal carriage of the causative S. aureus has not been identified in people working with the nude mice.

The pathogenesis of this infection is being studied.

PHS-6040

Objectives: To identify and characterize the causative Staphylococcus aureus strain(s) responsible for producing the abscesses. To examine the role of genotype and other factors in the expression of abscesses. To identify and develop microflora which will inhibit the responsible Staphylococcus aureus.

Methods Employed: Standard microbiological procedures.

Major Findings: The predominant phage pattern is 42E. Most nude mice carry the organism in their G-I tract but only a few develop abscesses.

Significance: Staphylococcal infections are a significant problem in the management of the NIH nude mouse resource as well as other colonies of nude mice. Because the colony has a limited and defined microflora antibiotics cannot be used to correct this problem. Short of surgical rederivation, manipulation of the microflora appears to be the only workable solution.

Proposed Course: Continuation

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH

DIVISION OF RESEARCH SERVICES

NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT FY 1981

Dr. Murray Eden, Chief

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10001-13 BEI

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Pharmacokinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Dedrick	Chief	ChES BEIB DRS
	J.M. Collins	Chemical Engineer	BEIB DRS
OTHER:	D.S. Zaharko	Pharmacologist	LCHPH NCI
	F. King	Associate Professor	Howard Univ.
	R.J. Lutz	Chemical Engineer	BEIB DRS
	P.M. Bungay	Chemical Engineer	BEIB DRS
	H.B. Matthews	Pharmacologist	NTP NIEHS
	I.G. Sipes	Assistant Professor	Univ. of Arizona
	C.E. Myers	Oncologist	CPB NCI
	M.F. Flessner	Chemical Engineer	US Coast Guard
	N. Bachur	Chief	LCB NCI
	J. Strong	Chemist	LCHPH NCI
	B. Smith	Neurosurgeon	SNB NINCDS

COOPERATING UNITS (if any)

LCHPH-NCI; LCB-NCI; SNB-NINCDS; CRD Program NIAMDD; M-NCI; NTP-NIEHS; CPB-NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

X(a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pharmacokinetic models are developed for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man. They provide a plausible set of equations that can be used to extrapolate data from animals to man and thereby improve chemotherapy, hemodialysis, and risk assessment.

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man to:

(1) Account for species differences in drug distribution.

(2) Provide a rational basis for extrapolating toxicity from animals to man.

(3) In conjunction with pharmacodynamics, provide a basis for optimizing cancer chemotherapy and chronic hemodialysis.

(4) Enable rational transfer of in vitro thermodynamic and kinetic data to in vivo cases.

(5) Predict effective dose schedules of anticancer drugs in individual patients with particular emphasis on intraperitoneal drug administration.

Methods Employed: Mathematical models are developed from physicochemical, physiological, and anatomical information and the principles of chemical reaction engineering. Resulting sets of differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings:

(1) The rate of disappearance of 5-fluorouracil from peritoneal fluid in the rat has been experimentally measured and mathematically modeled. The rate of disappearance was about 10X higher at 24 M than at 12mM. A distributed model has been formulated which incorporates concepts of diffusion with saturable metabolism and nonsaturable capillary uptake in the tissue surrounding the peritoneal fluid. At high concentration, the model suggests that uptake by blood dominates the rate. At low concentrations (linear metabolism), metabolism dominates since it is about 80X faster than blood flow removal. This model also predicts that the effective penetration depth into tissue is highly dependent upon concentration.

(2) A theoretical analysis of the role of the lung in pharmacokinetics has been completed. This work was stimulated by several recent collaborations involving drugs with very large total body clearance. The analysis emphasizes the role of the lung in relation to its anatomic position. Several examples have been developed which demonstrate that a relatively small amount of pulmonary activity can have a large impact.

(3) The pharmacokinetics of the radiation sensitizers misonidazole and desmethylmisonidazole in the perfused rat liver have been modeled. Kinetic data from in-vitro experiments have been incorporated into the model to successfully predict the rate of formation of desmethylmisonidazole from misonidazole in the perfused liver system.

(4) Drug entry into the central nervous system in generally restricted by the blood brain barrier. The Ommaya reservoir provides a convenient means for obtaining serial samples of cerebrospinal fluid. Several recent studies of anticancer drugs have employed this device in either monkeys or humans. Pharmackinetic analysis of the results of these studies is on-going, and should provide the basis for extendingd our limited knowledge of CNS kinetics.

(5) A pharmacokinetic model is being developed for 5-methyltetrahydromofolate (MTHHF) in the mouse, rat, dog, and monkey. MTHHF inhibits the growth of a variant of L1210 leukemia which is resistant to folate antagonists and is entering clinical trial to study its effect against MTX-resistant solid tumors. MTHHF is not metabolized in any of the species and is excreted into the urine and feces. The model indicates that the free drug is cleared at GFR in all species. Both kidney clearance and biliary clearance vary with body weight to the 0.8 power.

(6) A physiologic model is being developed for the environmental contaminant tetrachlorodibenzofuran (TCDF) in mice, guinea pigs, rats, and monkeys. TCDF is a contaminant in PCBs and is present in incinerator fly ash and flue gases. TCDF toxicity is highly species dependent. Metabolized TCDF is readily cleared to urine and feces. The liver, fat, and skin are major depots of TCDF in the body. A PCB-type model with a combined excretion term has been used to model the drug in all species.

(7) A distributed mathematical model has been developed to describe transport of uncharged water soluble substances between plasma and peritoneal fluid. The model includes diffusion and convectrion through peritoneal tissue, lymphatic uptake, and transport across blood capillaries, which are assumed to be distributed uniformly in the tissue. The model has been applied to experimental data for the trasnport of substances ranging in molecular weight from 180 to 160,000 Daltons in the rat, and model parameters have been estimated.

Significance: Drugs and other chemicals are tested for effect in animals, with the aim of extrapolating results to man. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with consideration of pharmacodynamic and cytokinetic events and drug interactions. Continued clinical emphasis through support of intraperitoneal procedures and other measures to overcome drug resistance. Increased emphasis on research designed to investigate distribution and metabolism of environmental contaminants and on methods for incorporating pharmacokinetics in models of risk assessment. Investigation of use of in vitro assays of chemical metabolism in conjunction with pharmacokinetic models for quantitative prediction of metabolism in vivo.

Publications:

Lutz, R.J., Dedrick, R.L. and Zaharko, D.S.: pharmacokinetics: an in-vivo approach to membrane transport. Pharmacol. Therapeutics 11:559-592 (1980).

Reprinted in International Encyclopedia of pharmacology and Therapeutics, Membrane Transport of Chemotherapeutic Agents, I.D. Goldman (Ed.), Pergamon, New York (In Press).

Speyer, J.L., Sugarbaker, P.H., Collins, J.M., Dedrick, R.L., et al.: Portal levels of hepatic clearance of 5-fluorouracil after intraperitoneal administration in man. Cancer Research 41:1916-1922 (1981)

Jones, R.B., Collins, J.M., MYers, C.E., et al.: High volume intraperitoneal chemotherapy with methotrexate in patients with cancer. Canc. Res. 41:55-59 (1981).

Collins, J.M. and Dedrick, R.L.: Contribution of the lung to total body clearance: linear and nonlinear effects. J. Pharm. Sci. (In Press).

Litterst, C.L., Collins, J.M., Lowe, M., et al.: Toxicity resulting from large volume intraperitoneal administrationof adriamycin in the rat. Cancer Treat. Rep.(In Press)

Monks, A., McManus, M.E., Collins, J.M., et al.: Non-linear pharmacokinetics of misonidazole in the perfused rat liver. Proc. Amer. Assoc. Cancer Res. (Abstract) 22:238 (1981).

King, F.G. and Dedrick, R.L.: Physiologic Model for the Pharmacokinetics of 2'deoxycoformycin in Normal and Leukemic Mice. J. Pharmacokin. and Biopharm. (In Press).

Collins, J.M. and Dedrick, R.L.: Pharmacokinetics of anticancer drugs. In Clinical Pharmacology of Antitumor Drugs, B.A. Chabner (Ed.), Saunders, Philadelphia (In Press).

Bungay, P.M., Dedrick, R.L., and Matthews, H.B.: Enteric Transport of Parent Chlordecone (Kepone®) in the Rat. J. Pharmacokin. Biopharm. (In Press).

Dedrick, R.L.: An Engineer's Perspective on Environmental Toxicology. 74th Annual AIChE Meeting. (In Press).

Dedrick, R.L.: Interspecies Dose-Response for Radiogenic Bone Cancer. Science (In Press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10002-16 BEI

PERIOD COVERED

October 1, 1980 to September 1981

TITLE OF PROJECT (80 characters or less)

Implant Device Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.W. Boretos	Physical Scientist	BEIB, DRS
OTHER:	W.S. Pierce	Associate Professor	Penn State University
	J. Doppman	Radiologist	CR, CC
	E. Glatstein	Chief	RO, NCI

COOPERATING UNITS (if any)

CR-CC; Pennsylvania Sate University, RO, NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to elucidate the interaction of biomaterials used for specific implants with the physiological environment and to explore specially prepared biomaterials and design features with respect to their suitability and performance in a variety of contexts. After removal from the host organism, implants will be examined for lipid absorption, changes in surface-free energy, and alteration of physical properties. Observations should include scanning electron microscopy, infrared spectroscopy, contact angle measurements, and energy dispersive X-ray analysis. Physical measurements will be made of tensile properties, flexural-fatigue resistance, electrical properties, hardness, density, coefficient of static and kinetic friction, hydrophilicity, and other surface and bulk properties.

Objectives: Elucidate the interaction of polymers, metals, and ceramics used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic composition of biomaterials is carefully controlled, and modifications are employed to enhance acceptability by the living system. After removal, implants are examined for lipid absorption, protein and/or calcium deposition, changes in surface-free energy, and alteration of physical properties. Observation techniques include SEM, infrared spectroscopy, contact angle measurements, energy dispersive X-ray analysis, and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied in vitro in a test apparatus. Electronic implants are examined periodically in vivo for changes in threshold levels, corrosion, and tissue activity. In vitro studies of the aforementioned are designed to accelerate fatigue testing and methods of improvement through heat treatment of the metal components undergoing stress. Surfaces of cathethers are modified using surface treatments of grafted polymers and copolymers to reduce drag through the blood vessels. These catheters are tested for burst strength, stiffness, tensile strength, and density. The basic composition is modified through compounding. Embolizing agents consisting of composites of polymers, ceramics, and metals are being devised for delivery through the catheter systems so as to block arteries and vessels in the treatment of lesions such as aneurysms and arteriovenous malformations.

Major Findings: Several hydrogel polymers can be applied to the surfaces of microcatheters to increase lubricity thereby minimizing resistance to movement through narrow and winding vessels.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart-assist devices, vascular implants, indwelling catheters, and subcutaneous uses.

Proposed Course: Extend experimental studies to further characterize the surface and bulk properties of biomaterials and, more specifically, determine their interactions with blood and subcutaneous tissue to facilitate development of better surfical implants.

Publications:

Boretos, J.W.: Encapsulation Considerations for Acute/Long Term Durability of Electronic Implants. In M. Szycher and W.J. Robinson (Eds.) Synthetic Biomedical Polymers: Concepts and Practices. Technomics Publishing Co., Westport, Conn. 1980, pp. 187-200.

Boretos, J.W., Terek, R.M., Girton, M.E. and Doppman, J.L.: Cohesive and Frictional Reduction of Intra-arterial Microcatheters. Proceedings of the 33rd Annual Conference on Engineering in Medicine and Biology, Washington, DC, September 1980, p. 74.

Boretos, J.W., Dengler, W.C., Terek, R.M., Edwards, K.J., Jr., Wilkins, J.F., Girton, M.E. and Doppman, J.L.: Integral Balloon Catheter for Interventional Radiology. Proceedings of the 33rd Annual Conference on Engineering in Medicine and Biology, Washington, DC, September 1980, p. 159.

Goldstein, S.R., Jones, R.E., Sipe, J.J., Doppman, J.L. and Boretos, J.W.: A Miniature Toposcopic Catheter Suitable for Small Diameter Tortuous Blood Vessels. J. Biomed. Engr. 102:221 (1980).

Boretos, J.W.: Selection Criteria for Polymeric Implant Applications with Representative Modifications for Increased Acceptability. In Ghista, Reul and Rau (Eds.) Perspective in Biomechanics, Harwood Academic Publ., NY, 1981.

Boretos, J.W.: The Chemistry and Biocompatibility of Specific Polyurethane Systems for Medical Use. In D.F. Williams (Ed.), Biocompatibility of Clinical Implant Materials, CRC Press, (In Press).

Boretos, J.W. and Edwards, K.J., Jr.: Drug Delivery Through An Integral Microcatheter. Proceedings 16th Annual Meeting of association for the Advancement of Medical Instrumentation, Washington, DC, 1981, p. 17.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10007-07 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	B.A. Vern	Clinical Associate	CNB NINCDS
	W.C. Whitehouse	Electronics Technician	ADM CC
	N. Mutsuga	Visiting Fellow	CNB NINCDS

COOPERATING UNITS (if any)

CNB-NINCDS; AB-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Oxidative metabolism, as indicated by the fluorescence of nicotinamide adenine dinucleotide (NADH) and oxygen consumption, was assessed to investigate potassium ion kinetics in the cat brain. Research was conducted to determine if the potassium clearance process is active or passive after activation of the cortex. Investigations were also conducted to determine the applicability of the NADH fluorescence technique to exposed myocardium. Active work on this project was completed before September 30, 1977; additional papers were published in 1979 and 1980. One paper was also published this year.

Methods Employed: The NADH fluorescence at 470 nM is excited by illumination with ultraviolet light at 360 nM obtained from a high pressure Hg arc lamp. To compensate for blood volume changes within the field of interest, we developed and used a television fluorometer employing fluorescein dye as a reference. The technique, initially used for study of cat brain, was also applied successfully to exposed myocardium.

A potassium-sensitive microelectrode system was employed for measuring both extracellular and intravenous potassium ion levels.

Direct cortical oxygen consumption measurements were made by cannulation of the sagittal sinus and monitoring the flow rate and hemoglobin saturation of the blood flowing out of the sinus. The calculated oxygen consumption is proportional to the arterial-venous oxygen concentration difference multiplied by the flow rate.

For the Q_{10} experiments, the exposed cat hippocampus temperature was either elevated or lowered by use of a controlled temperature stream of artificial spinal fluid which flowed over the surface of the hippocampus. Surface temperature was monitored by a small thermistor probe.

Major Findings: The NADH dynamics observed in the myocardium are similar to those observed in the cortex.

Blood volume in transiently ischemic myocardial tissue may increase due to relaxed muscle tone.

Fluorescein fluorescence was found to be an excellent indicator of myocardial perfusion.

Agreement was found between an analytical model for potassium clearance and experimentally determined potassium kinetics. This agreement provided further evidence of the active clearance process previously suggested by Q_{10} measurements and the slowing of potassium clearance during periods of hypotension.

Publications:

Vern, B.A., Schuette, W.H., and Whitehouse, W.C.: Effects of Brain Stem Stimulation on Cortical NADH Fluorescence, Blood Flow, and O_2 Consumption in the Cat. Experimental Neurology, 71:581-600, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER 10 Z01 RS 10015-06 BEI

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Development of Miniature Catheter for Clinical Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. Shook	Mechanical Engineer	BEIB DRS
OTHER:	S.R. Goldstein	Chief	MES BEIB DRS
	J.L. Doppman	Chief	DR CC

COOPERATING UNITS (if any)

DR-CC

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	.8	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES x (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A miniature toposcopic catheter attached to the end of a 1-mm #5 French catheter has been developed for insertion in tortuous blood vessels as small as 1 mm in diameter and up to 30 cm long. Catheter tests in anesthetized dogs have been highly successful - the catheter is able to penetrate parts of the vascular system which are inaccessible by existing techniques. The apparatus has been redesigned to provide the reliability and convenience required for clinical use. The catheter will enable the delivery of embolizing agents or other therapeutic substances so that some procedures previously requiring surgery can be performed instead with catheters. Techniques of steering the catheter are being developed and efforts are in progress to allow aspiration of fluid from remote areas.

Objectives: Develop techniques and devices for inserting a miniature catheter into small tortuous vessels and steering it into selected branches.

Develop techniques and devices for delivering therapeutic materials into the catheterized vessel for clinical usage and to aspirate fluids from these locations.

Major Findings: An improved miniature topographic catheter capable of negotiating tortuous paths has been successfully tested in dogs and will soon be ready for clinical use.

Significance: Surgeons and radiologists have long sought techniques for catheterizing small diameter vessels separated from larger, easily catheterized vessels by long, narrow passages with numerous bifurcations. The capability would permit selective treatment of tumors, aneurysms, and other lesions with minimal danger to normal tissues. Delivery of embolizing agents and materials to stain tissue, as well as aspiration of fluid, are contemplated.

Proposed Course: Complete modifications of the previously developed system, perform dog tests and then use the system clinically. Develop techniques for aspirating fluids for diagnostic purposes. Develop steering techniques, test in animals, and incorporate into the existing system. Develop related devices and explore additional uses for the catheter.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10018-06 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Particulate Hydrodynamics in Porous Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
	M.E. O'Neill	Reader Mathematics	Univ. Coll., London

COOPERATING UNITS (if any)

Department of Mathematics, University College, London

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models are being developed to describe passive membrane transport through pores or intracellular gap junctions. The Taylor-Aris dispersion analysis is extended to treat combined Brownian motion and convection in a single pore. The solute particle dimension is assumed to be large compared to that of the solvent molecules and also appreciable in size compared to the lateral pore dimension. The latter condition implies strong "hindered diffusion" and related solute-membrane interaction effects. A key aspect of the analysis is a generalized Einstein relation for predicting axial and radial components of the diffusivity tensor from hydrodynamics solutions for resistance coefficients. Perturbation techniques are used to obtain asymptotic solutions to the hydrodynamic equations, and the method of moments is employed to analyze the solute continuity equation. Related hydrodynamic problems are also being considered, such as flow through constricted vessels.

Objectives: The objective of this project is to provide the basis for a rigorous, predictive continuum theory for passive transport phenomena in porous membranes, including such observations as "hindered diffusion". The development of solutions to hydrodynamic problems of interest in other areas of the biological and physical sciences is also considered.

Methods Employed: The essence of the approach to membrane transport is an extension of the Einstein continuum analysis for the Brownian motion of spherical molecules in dilute solutions. Einstein derived his predictive relation for the diffusion coefficient from the theoretical expression for the hydrodynamic resistance to translation of a rigid sphere through a homogenous viscous fluid of infinite extent. The continuum analysis for porous membranes begins with a single solute molecule in a single pore and assumes that the form of Einstein's relationship between the diffusion and resistance coefficients remains valid. However, the presence of the rigid pore wall, in general, increases the hydrodynamic resistance to translation and rotation of the solute relative to the fluid. The diffusivity is thereby decreased in magnitude until, in the limit, as the solute dimension becomes equal to the lateral pore dimension, the diffusion coefficient falls to zero. Where there is, in addition to diffusion, net movement of the fluid through the pore, the hydrodynamic interaction similarly affects the solute flux relative to the solvent flux. The project is concerned with deriving the requisite expressions for the resistance coefficients from hydrodynamic theory as well as developing analyses for diffusive and convective porous membrane transport.

The primary theoretical tools used in the hydrodynamic problems are regular and singular perturbation techniques (typically using the ratio of solute to pore dimensions as the asymptotic expansion parameter) and collocation techniques of the type developed by Weinbaum and Pfeffer.

The transport analysis has been approached using the Taylor-Aris type dispersion treatment and the method of moments for deriving expressions for the pertinent coefficients without directly solving the complete solute continuity equation (convective-diffusion equation).

Major Findings: We completed the derivation of expressions correct to the second order in the sphere-to-tube radius ratio for the pressure drop due to the presence of neutral spherical solutes in cylindrical pores. Numerical computations using these expressions is proceeding.

An analysis was begun for describing the axisymmetric settling of a toroidal particle inside a vertical fluid-filled tube.

Proposed Course: In addition to the models presently under study, it would be desirable to examine a situation in which the solute is a nonspherical body in order to determine how to handle partical orientation and rotational Brownian motion effects. An ellipsoidal solute would be the likely choice in terms of posing theoretically tractable problems. Another direction to pursue, which would greatly extend the range of applications for the theory, would be to incorporate into the present models nonhydrodynamic solute-membrane interactions such as electrostatic or London Van der Waals attractive/repulsive forces.

Significance: Channels (pores, slitlike gap junctions) represent one important type of transmembrane transport in biological systems. A rigorous conceptual and predictive framework for pore theory would be useful in clarifying relevant biological transport and would find wide applicability in engineering and physical science work pertaining to synthetic membranes.

Publications:

Bungay, P.M. and O'Neill, M.E.: The pressure drop along a tube due to an axisymmetric constriction. J. Colloid Interface Science 71(2): 216-236, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10027-05 BEI

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Development of Whole-Body Hyperthermia Instrumentation and Control System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	J. Bull	Senior Investigator	MC DCT NCI
	D. Lees	Staff Anesthesia	CC NIH
	R. Corsey	Electronic Engineer	BEIB DRS
	H. Tipton	Mechanical Engineer	BEIB DRS
	R. Smith	Nurse	MC DCT NCI

COOPERATING UNITS (if any)

MC-DCT-NCI; CC-NIH; MS-DCT-NIH

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Whole body hyperthermia is being studied at NIH as a possible means of treatment for cancer. This project includes development of an instrumentation and control system based on utilization of a Tektronix 31 programmable calculator, digital plotter, and interface for data acquisition. The esophageal temperature of the patient is regulated to 0.1°C accuracy by feedback control of the temperature of water circulating in a set of hyperthermia blankets. The NIH phase of this project was completed August 1980, however additional publications have been made.

Methods Employed: A Tektronix 31 programmable calculator is being used to acquire, record, and process data as well as to control water temperature of a set of hyperthermia blankets. The temperature of the water pumped through the blankets together with esophageal and rectal temperatures of the patient are processed by the calculator, which then develops temperature commands for the water temperature mixing valve. The mixing valve adds hot or cold water to the flow stream returning from the blankets as directed by the Tektronix digital interface unit so that heart rate, blood pressure, and temperature data could be processed by the system. The multiplexer module also provides commands from the calculator to the water mixing valve motor. Automatic cool-downs are programmed into the calculator in response to various out-of-limit conditions. The calculator functions in an interactive mode for entry of operational instructions.

Major Findings: The major finding from the use of the equipment is that it is possible to take the whole-body core temperature of patients to $42.0 \pm 0.1^{\circ}C$ for four hours on a biweekly basis without major difficulty. The finding suggests that hyperthermia treatment for cancer is practical. Currently, the system is being employed in conjunction with chemotherapy at the Herman Hospital, Houston, Texas.

Publications:

Smith, R., Bull, J.M., Lees, D.E. and Schuette, W.H.: Whole Body Hyperthermia: Nursing Management and Intervention. Cancer Nursing, pp. 185-189,June 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10034-04 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Three-Dimensional Histological Reconstruction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: S.B. Leighton Mechanical Engineer BEIB DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.5	.45	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A semi-automatic system for acquisition of three-dimensional structural information about histological material is being developed. The system should have significant speed and reliability advantages over present techniques using serial sections, although resolution may be limited. In brief, an embedded tissue block will be fixed relative to a scanning electron microscope imaging system, the surface of the block will be imaged and stored, and successive slices will be removed by a built-in microtome. Handling and registration of thin sections will thus be eliminated. Human and computer pattern recognition will transform the resulting set of images into a three-dimensional reconstruction.

Objectives: (1) To facilitate making schematic diagrams of neural networks. (2) To facilitate developmental studies of small organs and organisms. (3) To do three-dimensional reconstruction of biological structures.

Methods Employed: A miniature microtome has been designed to function within the vacuum chamber of a scanning electron microscope. The microtome is designed using flex hinges and a hydraulic drive for the knife and flex hinges and a combination pneumatic, lead screw, and piezolelectric drive for the specimen. The specimens are embedded in epon and the cut faces are coated with a thin layer of gold-palladium to prevent charging. The microtome is operated from outside the SEM by means of the hydraulic and pneumatic tubes passing through a vacuum feedthrough. The sections are removed with a small argon jet.

Major Findings: The microtome has been constructed and tested successfully within the SEM. Satisfactory images of squid fin nerves have been obtained. Resolution so far has been 600 Angstroms.

Significance: Neuroanatomists may be able to trace significant neural nets with sufficient ease to allow a statistically significant number of samples.Other biological studies may be materially aided.

Proposed Course: The system will be integrated with an existing computer for image processing for semi-automatic three-dimensional reconstructions. Improved embedding media will be tested to give an etched surface effect to improve resolution. An improved gold-ion deposition system will also be added.

Publications:

Leighton, S.B.: "A Miniature Microtome for Use Inside Scanning Electron Microscope", 1981 Advances in Bioengineering, ASME, NY, (In Press)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10041-04 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Flow Visualization Studies and Hemodynamic Events in Model Arteries

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Lutz	Chemical Engineer	BEIB DRS
OTHER:	R.L. Dedrick	Chief	ChES BEIB DRS
	D.L. Fry	Chief	H IR OD

COOPERATING UNITS (if any)

OD - IR - NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.4	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The appearance of atherosclerotic lesions at specific locations in the arterial tree has led many investigators to study the relevance of hemodynamic factors in atherogenesis. The purpose of this study is to investigate the patterns of flow in models of arterial geometry, to measure velocity profiles at several cross sections, and to seek correlations between fluid mechanic events and the development of atherosclerotic plaques. Various methods of flow visualization such as dye injection, neutrally buoyant microsphere tracers and laser illuminated light scattering particles are being used to study the flow patterns in arterial models as a function of various flow parameters such as Reynolds number, branch flow ratios, and pulsatility. Both still photography and high-speed cinematography record the flow phenomena. The electrochemical technique measures average mass transfer coefficients to the artery wall under conditions of steady and pulsatile flow.

Objectives: The objectives of this study are to visualize and record the various kinds of flow phenomena such as flow separation and secondary flow that may occur in complex flow channels that represent arterial geometry and to correlate the flow phenomena with the location of atherosclerotic plaques in experimental animals. The analysis will include a quantitative measure of the velocity profiles at various sites in the model arteries. In conjunction with these experiments, measurements will be made of the mass transfer coefficients to the walls of the model arteries under conditions of both steady and pulsatile flow.

Methods Employed: Several methods have already been shown to be useful for visualizing flow patterns in our model systems, and other methods can be tried. The electrochemical method of measuring mass transfer coefficients is being used in several model systems. The following flow visualization techniques are being used.

(1) Dye injection. At selected sites in the arterial model, small ports are drilled for insertion of #30 gauge hypodermic tubing, which is connected via PE 10 catheter tubing to a reservoir of colored dye. The end of the hypodermic tubing can be positioned at any radial location in the flow model and the dye slowly injected into the flow to mark the streamlines. The streamline patterns at several sites are then recorded using 35-mm still photography. Data obtained by dye injection into the flow indicate that the flow streamlines are skewed toward the side-arm branches exiting from the main (aortic) flow channel and that unusual patterns of backflow and secondary flow occur near the dorsal channel wall just opposite the branch orifices. These phenomena are governed by the fraction of the flow that exits out each daughter branch.

(2) Neutrally buoyant microspheres. This method employs a dilute suspension of 100- to 500-micron diameter polystyrene microspheres in a 20 to 25 percent glycerine/water solution, which serves as the test fluid in the flow model. The microspheres are dyed with a fluorescent dye and then illuminated with ultraviolet light making them clearly visible in the flow system. The path of the microspheres are photographed with high-speed cinematography as these neutrally buoyant particles move along with the fluid. In such a manner, the direction and velocity of fluid elements can be determined. This method gives an overall view of the flow patterns throughout the bulk of the fluid flow.

(3) Laser Doppler velocimetry. When light is scattered from a moving object, a stationary observer will see a change in the frequency of the scattered light (Doppler shift) proportional to the velocity of the object. This Doppler shift is used to measure the velocity of particles at various locations in the fluid. From the particle velocity, the fluid velocity is inferred. A laser is used as the light source because it is easily focused and coherent. This method allows us to determine, quantitatively, the velocity profiles at various positions in the arterial model. Numerous profiles have been recorded in both steady and sinusoidal flow at various flow rates.

By passing the thin collimated laser beam through a cylindrical lens, a source of plane illumination can be created which can be used to visualize a specific narrow cross section in the flow channel by observing its light scattering effect from small

particles that move with the fluid. This technique exhibits, in two dimensions, various flow patterns like stream lines and separation eddies.

Major Findings:

Wall Shear Rates: Wall shear rates were measured by the electrichemical technique in a two-branch model representing the celiac and superior mesenteric branches in the canine aorta. Shear patterns were similar to those found earlier in a canine aortic cast of this region. The shear rate in the celiac branch varied considerably just inside the branch entrance as celiac flow was varied. Flow separation was not detected in this branch. Shear patterns inside the celiac branch were not sensitive to flow rates in the adjacent mesenteric branch. Shear rates on the aortic side of the celiac flow divider lip (which starts the approach to the mesenteric divider) was nearly linearly related to celiac flow but insensitive to mesenteric flow. Dorsal shear rates were much lower than ventral shear rates.

Velocity Profiles: Velocity profiles were obtained in two diametrical planes, one in the plane of branches (sagittal), the other perpendicular to that plane (lateral). The entrance to the model has a fully developed parabolic profile, but the sagittal profiles became skewed toward the branch side of the model as one progressed further downstream near and beyond the branches. Skewness increased with increasing branch flow rate. Flow separation and flow reversals were seen with the profile measurements at the proper flow conditions. Pulsatile flow representing a cardiac waveform generated velocity profiles distinctly different from steady flow results. Pulse profiles were very blunt and only showed reverse flow phenomena when the total flow rate was negative.

Wall Mass Transfer: Wall mass transfer coefficients were measured using the electrochemical technique for steady, sinusoidal, and pulsatile flow. For steady flow, the mass transfer patterns throughout the artery were the same as the shear patterns calculated previously since these two phemonena are interrelated. Pulsatile flow enhanced mass transfer from 50% to 100% in regions which would normally exhibit flow separation under steady flow conditions. In other regions, the average mass transfer coefficient for pulsatile flow was similar to that for steady flow at the same average flow rate.

Significance: Elucidation of the role of hemodynamics on the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease. Certain biological evidence suggest that areas of increased plaque formation may correlate with areas frequently exposed to disturbed flow, for example, flow spearation, or to relatively stable flow patterns that change direction and magnitude periodically throughout the day with varying metabolica and blood flow demands. This study should demonstrate various types of flow patterns that can occur in arterial systems as a function of changing flow parameters. Likewise, the mass transfer of blood-borne constitutents like oxygen or lipoproteins can be affected by the flow patterns in various regions near the artery wall. An imbalance n the mass transfer of these elements can cause either vascular damage or excess accumulation of lipids which can eventually lead to a pathological state in the artery wall.

Proposed Course: (1) Study the flow patterns in these models using the various techniques described above as a function of several flow parameters such as Reynolds number, branch flow ratio, and flow pulse frequency. (2) Correlate these findings with those of our previous experiments on wall shear stress in similar models. (3) Determine the mass transfer coefficients to the arterial wall as a function of various Schmidt numbers under conditions of steady and pulsatile flow. (4) Correlate all hemodynamic evidence with incidence of lesions in experimental animals.

Publications:

Lutz, R.J., Menawat, A., Hsu, L., Zrubek, J.: Fluid Mechanics and Boundary Layer Mass Transport in an Arterial Model During Steady and Pulsatile Flow. In Gross, J. and Tarbell, J. (Chairmen), Biology Rheology and Fluid Mechanics, 74th Annual AIChE Meeting, New Orleans, Louisiana, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10043-04 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Fiber Optic Probes/Oxygen

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB, DRS

COOPERATING UNITS (if any)
H-IR-MH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.70	.70	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The development of an implantable fiber-optic PO_2 probe for clinical and physiological measurements has continued through this year. The fiber-optic pH probe we developed earlier i a general model for the current design. The PO_2 probe is an optical device for measuring oxygen tension in the body, based on oxygen's effect of decreasing the fluorescence of certain dyes.

Objectives: Develop an oxygen sensor for physiological implantation to be used in studies of oxygen transport during exercise, and clinical Po_2 measurements.

Methods Employed: A fiber optic measurement of dye-indicator response to oxygen by fluorescence quenching.

Significance: Po_2 measurements are fundamental to understanding and control of oxygen transport in research and clinical investigations. Measurements on withdrawn blood samples lack convenience, reliability, and relevance to many situations of interest. Indirect estimation of Po_2 using spectrophotometric measurements of hemoglobin oxygenation and the concentration-pressure transfer function (blood oxygen saturation curve) is subject to too many uncertain variables. Development of a fiber optic Po_2 probe would represent a significant advance in the ability to directly and continuously measure blood and tissue oxygen. A satisfactory electrode for general use has never been developed, and the fiber optic approach offers some distinct advantages in small size, flexibility, and safety.

Major Findings and Proposed Course: Previous work involved solving the problems of finding a suitable dys, a suitable support for the dye, and an oxygen permeable containment system, along with evaluation of the performance of probe construction methods.

The current year has been partly devoted to development of an associated instrumentation system for the probe, as it became evident that further development and evaluation of the probe depended on this. Following this, the latter part of the year has mainly involved work to improve the probe and test its suitability for use under physiological conditions. This will continue into the next year.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10050-03 BEI

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Positron Emission Tomography Scanner

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. DiChiro	Section Chief	SN NINCDS
OTHER:	R.A. Brooks	Senior Staff Fellow	SN NINCDS
	V.J. Sank	Research Physicist	SN NINCDS
	W.S. Friauf	Electronics Engineer	EEES BEIB DRS
	S.L. Leighton	Mechanical Engineer	MES BEIB DRS
	H.E. Cascio	Electronics Engineer	EEES BEIB DRS
	G.L. Hemphill	Electronics Technician	EEES BEIB DRS

COOPERATING UNITS (if any)

SN NINCDS

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

EEES, MES

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

x (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

[x] (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A custom PET scanner is being developed to provide compromises between resolution, sensitivity, count rate capability, and cost that are optimal for human neurological research requirements at NIH.

Objectives: Design and have built a PET scanner with higher resolution than other custom or commercial machines, but without excessive compromise of sensitivity or count rate capability.

Methods Employed: The design will feature a large number of BGO detectors more tightly packed in a smaller ring than other designs, with electronic advances to shorten the coincidence window to a minimum, thus easing the random coincidence problem which is aggravated by a small ring. A novel detector motion has been developed to further improve resolution.

Major Findings: System integration of the major sub-systems has been under way for the past year. These sub-systems include the gantry, ring assembly, electronics, computer, display system, and software. Numerous problems have been encountered and resolved. All indications are that the original performance specifications should be realized.

Significance: PET imaging with a variety of positron emitting tracers allows many metabolic processes to be studied spatially. The new scanner will increase the spatial resolution which currently limits the potential of the approach.

Publications:

Brooks, R.A., Sank, V.J., DiChiro, G., Friauf, W.S., and Leighton, S.B.: "Design of a High Resolution Positron Emission Tomograph: The Neuro-PET. Journal of Computer Assisted Tomography 4(1): 5-13, February, 1980.

Brooks, R.A., Sank, V.J., Friauf, W.S., Leighton, S.B., Cascio, H.E., and DiChiro, G.: Design Considerations for Positron Emission Tomography. IEEE Transactions Biomed. Eng. Vol. BME-28, No. 2, Feb. 1981, pp. 158-177.

Invention Reports: Four have been submitted.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10053-03 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Membrane Based Sampling Systems for in In Vivo and In Vitro Kinetic Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	J.P. Froehlich	Senior Investigator	GRC NIA
	R.L. Berger	Section Chief	LTD NHLBI
	J. Fenstermacher	Section Chief	LCHPH DCT
	R.L. Dedrick	Section Chief	ChES BEIB DRS

COOPERATING UNITS (if any)

Gerontology Research Center-NIA; Laboratory of Technical Development-NHLBI; Laboratory of Chemical Pharmacology-DCT.

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES X (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Synthetic membranes are being utilized in kinetics studies to provide a means for continuous sampling of the liquid phases from systems in which a dispersed particulate phase is suspended in the liquid phase. In one application sampling equipment is being developed for in vitro study of calcium ion transport and calcium-ATPase activity in suspension of sarcoplasmic reticulum vesicles prepared from homogenates of rabbit muscle. In a second application a study of the mammalian blood-brain-barrier permeability is being aided by the development of an apparatus incorporating a sampler in an arteriovenous ex vivo shunt. In the latter plasmapheresis application pooling the plasma filtrate yields a single sample from which the plasma concentration times time integral can be evaluated for a chemical administered to the animal. Such sampling systems can be useful for the study of the kinetics of other fluid phase systems for which a membrane can be found which is permeable to one chemical of interest but impermeable to another necessary reagent or sink. Thus, other applications might be found in the areas of enzyme kinetics, pharmacokinetics, and the membrane transport of vesicle and cell suspensions.

Z01 RS 10053-03 BEI

Objectives: The principal objective is the development of the capability for fluid sampling based upon synthetic membrane technology. In many potential applications sampling by filtration or ultrafiltration may be more appropriate than alternative sampling techniques. Ultrafiltration membranes allow the formation of samples representative of the free concentration of small soluble substances. These membranes will retain within the system under study macromolecules and those substances which are bound to them as well as colloidal or cellular components of the system. Other applications may call for the use of larger pore diameter membranes of, for example, macromolecules are to be sampled as well.

Methods Employed: The sampling system generally consists of three elements: (1) a module or modules containing sampling membranes, (2) sample collection equipment, and (3) a means for controlling the rate of production of sample. The membrane module is designed so that the membrane forms a part of the wall of the channel through which the liquid to be sampled flows. Only a small fraction of the liquid is diverted across the membrane to form the sample. The sample is produced as a consequence of a difference in pressure imposed across the membrane. The rate of production of the sample is regulated either by controlling the transmembrane pressure difference or through use of a sample metering pump.

Significance: Membrane sampling is being applied to studies of the transport of calcium ions across sarcoplasmic reticulum (SR). The transport studies are performed in vitro on a suspension of SR vesicles in buffer; the vesicles being created by homogenizing rabbit muscle. The kinetics of calcium uptake by or efflux from the vesicles can be followed by monitoring the appearance or disappearance of calcium from the suspending medium. Also, changes in levels of ATP and inorganic phosphate can be used to infer the kinetics of the calcium dependent membrane ATPase. The membrane in the sampler retains the vesicles (which are thought to be in the range of 0.1-0.5 m in diameter), so that the sample is representative of the suspending media.

A second application concerns in vivo studies of transport across the blood-brain-barrier. The initial objective is the determination of the barrier permeability to selected marker substances. In these experiments a sampler is connected in line with an extracorporeal arteriovenous shunt. By continuously and steadily drawing off a fraction of the shunt flow through the sampler membrane, one can integrate over time the concentration of the marker substances present in the plasma. The value of the integral, together with a determination of the amount of the substance taken up by the brain over the same time interval, permits a determination of a permeability-area transport coefficient for certain substances, such as potassium ion and x-amino isobutyric acid. A membrane which retains blood cells is of use in studies in which the transport of the substance into blood cells is sufficiently slow that the cells cannot be considered in equilibrium with the plasma. Use of ultrafiltration membranes may permit determination of the free concentration - time integral, rather than the integral for total plasma concentration, in circumstances of significant binding to plasma proteins.

The in vivo sampling technique can be applied to other acute pharmacokinetic studies for which the plasma concentration-time integral can be of use.

Major Findings: A premise underlying the concept of filtration sampling is that the marker substance appears in the filtrate (sample) solely because it is carried convectively across the membrane. However, in kinetic experiments in which the concentration of the marker on the upstream side of the membrane changes sufficiently rapidly with time, appreciable marker concentration gradients can be created across the membrane. Marker diffusion across the membrane can diminish or augment the amount of marker present in the sample. If the filtrate flow rate is sufficiently high or the diffusivity of the marker is small the diffusional contribution should be negligble compared to that from convection. We have been simulating the in vivo animal pharmacokinetic experiments using radiolabeled markers and a sheet membrane module in an in vitro set-up. Under the range of conditions investigated the sample has been representative of the rententate for nonbinding markers which suggests that diffusional artifacts should be negligible. We have begun the in vivo experiments using rabbits. The first substance being investigated is sucrose - a neutra nonbinding extracellular marker.

Other Activitites: Sponsored sessions on Synthetic Membrane Technology, national Institutes of Health Instrumentation Symposium, December 10-12, 1980; presented review "Current Applications in Biomedical Research".

Publications:

Dedrick, R.L. and Bungay, P.M. Meeting Report on the Synthetic Membrane Technology Sessions, 1980 National Institutes of Health Instrumentation Symposium

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10055-03 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Breath by Breath Analysis of Computer Controlled Exercise Stress Testing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
OTHER:	W. Schuette	Chief	ACES BEIB DRS
	T. Talbot	Mechanical Engineer	ACES BEIB DRS
	H. Tipton	Mechanical Engineer (Tech.)	ACES BEIB DRS
	R. Winslow	Sr. Scientist	IR-CL-NHLBI

COOPERATING UNITS (if any)
IR-CL-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.4	0.1

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In recent years exercise stress testing has become an important diagnostic tool. Most testing of this type is confined to cardiac studies. This system has been developed in order to assess the ability of the subject to transport and exchange oxygen and carbon dioxide between the atmosphere and the cells of the body. A large number of pathophysiologic states limit one's ability to perform these functions efficiently. With this system the anaerobic threshold of the subject during exercise can be detected non-invasively by breath-by-breath respiratory analysis. Oxygen Uptake, Carbon Dioxide Production, Respiratory Minute Volume, Respiration Rate, Heart Rate, and Respiratory Quotion are displayed as a function of Work Rate.

Z01 RS 10055-03 BEI

Objectives: To develop a system to analyze the respiratory quotient vs. work rate curve during exercise stress testing in order to determine the anaerobic threshold.

Methods Employed: A Tektronix 4051 programmable calculator and custom designed synchronous integrators and multiplexor has been used to produce breath-by-breath analysis of respiratory quotient as a function of work rate.

Significance: Correlation of the onset of anaerobic metabolism with work level provides a useful clinical measure of the general condition of the hematology patients under study. This method provides a better means of evaluating the efficacy of therapeutic measures.

Proposed Course: To add a pressure transducer to the mouthpiece in order to obtain respiratory power and work.

Publications:

Talbot, T.L., Thibault, L.E., Schuette, W.H., Winslow, R.M., and Tipton, H.W.: Breath-by-breath gas analysis during exercise stress testing. Advances in Bioengineering, 1979.

Schuette, W., Thibault, L., Talbot, T., and Tipton, H.: Synchronous integration - a method for the rapid determination of the mean value of pulsatile physiological signals. Proc. AAMI 15th Annual Meeting, San Francisco, April 13-17, 1980, p. 184.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10060-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Analytical High Voltage Electron Microscopy and Image Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.D. Leapman	Physicist	BEIB DRS
OTHER:	C.E. Fiori	Physical Scientist	BEIB DRS
	A.F. LeRoy	Chief, Micro. Group	BEIB DRS
	E. Silbergeld	Neurotoxicologist	ETB IRP NINCDS
	J.L. Costa	Staff Physician	CNB NIMH
	K.E. Gorlen	Electronics Engineer	CSL DCRT
	E. Pottala	Electronics Engineer	LAS DCRT
	C.R. Swyt	Physicist	BEIB DRS
	L.K. Barden		CSL DCRT
	J.S. DelPriore		CSL DCRT
	P.S. PLexico		CSL DCRT
	M.A. Douglas		LAS DCRT
	C.C. Gibson	Electronics Engineer	BEIB DRS
	Ray L. Ornberg		
	T. Reese		

COOPERATING UNITS (if any)

Computer Systems Laboratory, DCRT, NIMH, NINCDS; NINCD

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A number of features have been added to the Hitachi H700H TEM-STEM electron microscope and to the Electron Energy Loss Spectrometer (EELS). New alignment controls have improved the signal and energy resolution of the EELS making possible the study of some biological samples. These include dense bodies contained in blood platelets and inclusions in bacteria, where the light elements N and O as well as P and Ca have been detected. The addition of a liquid nitrogen cold stage has enabled 30nm diameter areas to be proved without contamination build-up, which had previously been a serious problem.

An annular detector has been installed for dark-field STEM imaging and it is planned to use this for contrast enhancement in unstained samples. Descanning of the EELS spectrometer has almost been completed and this will allow elemental mapping. Images will be digitized, stored on disk and displayed on a DeAnza graphics system linked to the PDP 11/60 computer. Considerable software has already been developed to process EELS and EDX spectra, which can now be loaded automatically into the main computer from the Kevex 7000. Other interfacing to the H7000H microscope should soon permit direct computer control of the EELS spectrometer as well as various new imaging modes to be implemented.

Objectives: To investigate how Electron Energy Loss Spectroscopy and Energy Dispersive X-ray spectroscopy can be exploited to carry out elemental microanalysis, and to establish how these methods can be combined with new imaging techniques.

Experimental Techniques: A 200 keV electron microscope is utilized to probe microvolume of thin biological samples. Elements are detected by recording their characteristic ionizations either using EDX where the de-excitation of the ionized atom causes x-ray emission, or using EELS where the ionization events are observed in the energy losses of the incident electrons.

Significance: EEELS permits the microanalysis of the light elements which are difficult to detect by any other means. EDX spectroscopy is complementary to EELS and together the techniques allow the investigation of a wide range of biological problems.

Proposed Course: To study in detail the application of Analytical Electron Microscopy in biology.

Publications:

Leapman, R.D. and Swyt, C.R.: Microanalysis of Ca and P biology using EELS. Proc. 39th EMSA Meeting, Atlanta (1981) Baton Rouge, G.W. Bailey, (Ed.), p.636.

Leapman, R.D. and Swyt, C.R.: A practical method for removing plural scattering from core edges. Proc. 39th Annual EMSA Meeting, Atlanta (1981) Baton Rouge, G.W. Bailey, (Ed.), p. 196.

Grunes, L.A., Leapman, R.D., Ray, A.B. and Silcox, J.: Some Observations on Core Edge Fine Structure and Orientation Dependent Effects in Inelastic Electron Scattering. Proc 39th Annual EMSA Meeting, Atlanta (1981), Baton Rouge, G.W. Bailey (Ed.), p. 178.

Leapman, R.D., Grunes, L.A., Fejes, P.L. and Silcox, J.: Extended Core Edge Fine Structure in Electron Energy Loss Spectra. In "EXAFS spectroscopy: Applications and Techniques", B.K. Teo and D.C. Joy (Eds.), Plenum Press, New York (1981), pp. 217-240.

Leapman, R.D. and Grunes, L.A.: Anamolous L_3/L_2 White-Line Ratios in the 3d Transition Metals. Physical Review Letters 45:397 (1980).

Leapman, R.D. and Grunes, L.A.: Microcharacterization of some Metals and their oxides using EELS Fine Structure. Proc. 7th European Congress on Electron Microscopy 3:70, The Hague (1980).

Grunes, L.A. and Leapman, R.D.: Optically Forbidden Excitation of the 3s subshell in the 3d transition elements. Phys. Rev. B22:3778 (1980).

Leapman, R.D. and Swyt, C.R.: EELS under conditions of plural scattering. Analytical Electron Microscopy - Proceedings of AEM Workshop, Vail, R.M.Geiss (Ed.)

Rez, P and Leapman, R.D.: Core loss shape and cross section calculation. Analytical Electron Microscopy - Proceedings of AEM Workshop, Vail, R.H. Geiss (Ed.)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10061-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Automated Scanning Electron Beam X-ray Microanalysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.E. Fiori	Physical Scientist	BEIB DRS
OTHER:	A. LeRoy	Chief, Micro. Group	BEIB DRS
	C.R. Swyt	Physicist	BEIB DRS
	K.E. Gorlen	Electronics Engineer	DCRT
	C. Merril	Biochemist	L GCB NIMH

COOPERATING UNITS (if any)
CSL, LAS, DCRT

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Due to budgetary constraints imposed during this reporting period it has not been possible to acquire the necessary hardware to interface the microprobe to out PDP 11-60 computer as projected in the last report. Consequently the emphasis of our work shifted to casting into computer programs those algorithms required to convert raw x-ray intensity data into chemical concentrations. These programs include a procedure to unravel spectral overlap, a Monte Carlo procedure to examine the production of x-rays from irregular specimens such as liquid microdroplets and a procedure to perform matrix corrections with a strong emphasis on biological applications. The programs are required to obtain quantitative chemical information from biological samples and are not generally available. The program to correct for the effects of spectral overlap has been completed and reported on. The other two programs are in advanced stage.

Work has been done on developing a new class of standard reference material for biological microanalysis. The material is comprised of Lithium borate glass doped with biologically relevant elements such as Mg, Al, Si, P, S, Cl, K, Ca . . . The glass has the interesting property of having a nearly identical matrix as biological material in terms of the electron and x-ray physics. Consequently, more accurate analysis is possible. A paper has been written on this work and has been accepted by the Journal of Microscopy.

Preliminary collaborative work has been don with Dr. Carl Merril of the Laboratory of General and Comparative Biochemistry, Institute of Mental Health. This work involves the determination of trace metals in the protein spots isolated by two dimensional gell electrophoresis. This work will continue.

Objectives: To provide a capability of performing elemental microanalysis on both bulk and thin biological specimens utilizing focussed electron beam induced X-ray spectroscopy.

Methods Employed: A focussed 2-50 keV electron beam is utilized to photoionize microvolumes (containing as small as 10^{-18} grams of matter) of biological specimens. By performing X-ray spectroscopy utilizing Bragg angle X-ray spectrometers, on the X-rays leaving the photoionized volume of the specimen it is possible to perform elemental microanalysis.

Significance: Electron beam microanalysis permits the solution of certain biological problems which would be difficult, or impossible, by other means.

Proposed Course: To apply the technique to biological research and to study in detail the problems involved in this application.

Publications:

Fiori, C.E., Swyt, C.R. and Gorlen K.E.: Application of the Top-Hat Digital Filter To A Nonlinear Spectral Unraveling Procedure in Energy Dispersive X-ray Microanalysis. Proc. of Microbeam Analysis Society. 1981, pp. 320-324.

Fiori, C.E. and Newbury, D.E.: The Operation of Energy Dispersive Detectors in the Analytical Electron Microscope. Analytical Electron Microscopy. R. Geiss (Ed.), San Francisco Press, In press.

Fiori, C.E., Gorlen, K.E. and Gibson, C.G.: Comments on the Computerization of an Analytical Electron Microscope. Proc. 39th Annual Meeting of EMSA, 1981, pp. 246-249.

Fiori, C.E.: Electron Beam Microanalysis: Several Instrumental Developments Germane to Biology. Journal of Histo-Cyto Chemistry, 29, pp. 1029-31, 1981.

Fiori, C.E. and Blackburn, D.B.: Low Z Glass Standards for Biological X-ray Microanalysis. Accepted by Journal of Microscopy.

Heinrich, K.F.J., Newbury, D.E., Myklebust, R.L. and Fiori, C.E. (Eds.), Energy Dispersive X-ray Spectrometry. National Bureau of Standards, Special Publication 604 U.S. Goverment Printing Office, pp. 1-443.

The following four papers in the preceding book:

Fiori, C.E., Myklebust, R.L. and Gorlen, K.: "Sequential Simplex: A Procedure for Resolving Spectral Interference in Energy Dispersive X-ray Spectrometry", p. 233.

Fiori, C.E., Newbury, D.E. and Myklebust, R.L.: "Artifacts Observed in Energy Dispersive X-ray Spectrometry in Electron Beam Instruments - A Cautionary Guide", p. 315.

Myklebust, R.L., Fiori, C.E. and Heinrich, K.F.J.: "Spectral Processing Techniques in a Quantitative Energy Dispersive X-ray Microanalysis Procedure (FRAME C), p. 365.

Fiori, C.E. and Swyt, C.R.: "Energy Dispersive Detectors - A Bibliography (1981)", p. 417.

Mannis, M.J., Fiori, C.E., Krachmer, J.H., Rodriquez, M.M. and Pardos, G.: Keratopathy Associated with Intra-Corneal Glass", Archives of Opthalmology, Vol. 99, May 1981, pp. 850-852.

Goldstein, J.I., Newbury, D.E., Joy, D.C., Fiori, C.E., Echlin, P. and Lifshin, E.: Scanning Electron Microscopy and X-ray Microanalysis: A Text for Biological, Geological and Materials Scientists. Plenum Press, (In Press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10062-02 BEI

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

IEEE-488 General Purpose Interface Bus Program Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: T.R. Clem Electronic Engineer EEES BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES x (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The ability to produce instrumentation systems using several individual instruments interconnected via the IEEE-488 General Purpose Interface Bus (GPIB) is being developed. With the cooperation of the BEIB-SERP a variety of bus-compatible instruments is being acquired to complement this ability.

Z01 RS 10062-02 BEI

Objectives: Develop expertise in the Branch in the use of IEEE-488 GPIB-compatible instruments and controllers. Recommend types of bus-compatible instruments for acquisition by the BEIB-SERP.

Methods Employed: Prototype or temporary systems are assembled from equipment available in the rental program. Prototype systems are assembled to prove feasibility of techniques prior to the design of dedicated systems. Temporary systems are used either to satisfy short-term instrumentation needs or to solve problems which require a quick response. A system was configured in the laboratory of Dr. Phil Ross, LMB, NIADDK, to temporarily replace a piece of equipment that has failed and needed repairing. By being able to set-up a bus-oriented system in less than two days as a substitute, there was virtually no disruption to the experiments in progress while the primary equipment was being repaired.

Significance: The capability of assembling an instrumentation system with a controller and GPIB-controlled instruments allows the EEES to provide a rapid response to an investigators call for instrumentation. By assembling a system with "off-the-shelf" instruments from the SERP, the cost of a special-purpose measurement or control system can be kept quite low. If the experiment is a short-term project the instruments can be returned to the SERP with virtually no expenditures, by the investigator, for equipment.

Proposed Course: Maintain state-of-the-art capability in the field of bus-compatible instruments and controllers. Seek to make this capability better known and understood around NIH.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10063-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Digital Thermistor Thermometer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.R. Clem	Electronics Engineer	EEES BEIB DRS
OTHER:	R. Berger	Section Chief	LTD NHLBI

COOPERATING UNITS (if any)
LTD, NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

High resolution and high accuracy thermistor thermometers, using microprocessors as control components, are being developed. These units are suitable for process control and data logging uses in the laboratory.

Z01 RS 10063-02 BEI

Objectives: Design and construct a series of high resolution, high accuracy (better than $\pm$ 0.01°C) thermometers using precision thermistors as sensing elements and digitizing the results for process control and/or data logging.

Methods Employed: The thermometers are each designed around a microprocessor and high resolution digital-to-analog and analog-to-digital convertors. A known excitation current is applied to the thermistor and the resultant voltage is read. The power level to the thermistor is controlled at a constant value for a minimum of self-heating error. The resistance of the thermistor is calculated and the corresponding temperature is derived from a look-up table which is generated for each thermistor individually.

Significance: These instruments provide high accuracy laboratory thermometers for precision temperature measurements.

Proposed Course: Design additional thermometers with emphasis on different features, i.e., speed, compactness, etc.

Publications:

Berger, R.L., Clem, T., Gibson, C., Siwek, W., and Sapoff, M.: A Digitally Linearized Thermitor Thermometer Referenced to IPTS-68". Clin. Chem. 26/13, 1813-1815, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10064-02 BEI

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Indirect Blood Pressure Measurements in Laboratory Animals Using Oscillometry

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.C. Walker	Mechanical Engineer	BEIB DRS
	J.E. Pierce	Chief, LAMSS, OD	NHLBI

COOPERATING UNITS (if any)

NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Currently there are no reliable indirect methods of measuring blood pressure in dogs. Traditional techniques, used in humans, are unsatisfactory primarily because they require the placement of a transducer over the artery being monitored.

Because of the unreliability of traditional techniques we have been investigating a technique called oscillometry. Oscillometry is a method of measuring blood pressure by analyzing the pulse pattern of the cuff pressure oscillations.

In practice, a cuff is placed around a limb and inflated to a pressure above systolic and then slowly deflated. While the cuff is being deflated the amplitude of oscillation in cuff pressure, produced by the arterial pulse beneath the cuff, is monitored. Systolic pressure is indicated by the first significant increase in oscillation amplitude. Diastolic pressure is indicated as the lowest cuff pressure at the point of maximum oscillation in cuff pressure. Currently most investigators using this technique take the point of maximum oscillation to indicate mean arterial pressure.

Z01 RS 10064-02 BEI

Objectives: The primary objective of this project is to develop an instrument to indirectly measure peripheral arterial blood pressure in laboratory animals.

Methods Employed: Anesthetized and awake studies were performed on laboratory dogs and pigs. Simultaneous direct arterial and indirect oscillometric cuff pressure measurements were obtained. A laboratory simulation of the oscillatory mechanism has also been employed.

Significance: Animal surgery labs and other laboratories or veterinarian offices could use an indirect device on a daily basis. For various laboratory studies monitoring blood pressure in awake animals is very desirable, particularly with protocols involving atherogenic diets, and drug therapy. Another area of application would be in screening animals for hypertension research. For surgical procedures, an indirect technique will allow blood pressure monitoring before and during induction of anesthesia.

Major Findings: The results of 19 dog experiments and many laboratory simulations indicate that oscillometry measures systolic and diastolic pressures but not the mean arterial pressure (contrary to previous interprelations of the measurement). Future efforts will be directed toward designing an automated oscillometric instrument.

An automated version of the manual instrument, used in the above studies, is currently being tested using a Tektronix 4050 series computer.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10065-01 BEI

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 charecters or less)

Transient Response of Micro-Calorimeters Using R-C Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. P. Mudd	Biomedical Engineer	BEIB, DRS
OTHER:	R. L. Berger	Section Chief	LTD, NHLBI

COOPERATING UNITS (if any)

LTD, NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES x (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The behavior of microcalorimeters lies between that of true adiabatic or bomb calorimeters and isothermal calorimeters. The location between these extremes depends upon a compromise involving many criteria but most importantly, time constant and sensitivity. The use of an R-C model of the system and Laplace transform techniques will allow us to study the transient behavior of the system to a variety of inputs, and to achieve optimized performance for specific applications of the calorimeter.

Objective: The objective of the analysis is to develop a model which can be used to predict the calorimeter's performance. If the model predicts the calorimeter's response to pulse and step inputs, it can be used as a design aid in subsequent redesigns and optimizations for specific applications.

Significance: To date, the model agreement with experimental data for pulse and step inputs is very good. In addition, the model has shown that the air gap between the cell and cell holder is the largest source of uncertainty in the instrument. Thus, the model has identified a key parameter as the major source of error in the calorimeter.

Proposed Course: By using the model, we have designed a new configuration for the sensor which eliminates the air gap by utilizing one thermopile instead of two. The new design should have greater sensitivity than the two thermopile configuration with no increase in rise-time.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10066-02 BEI

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Egyptian Training Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. P. Mudd	Biomedical Engineer	BEIB, DRS
OTHER:	H. W. Metz	Assistant Branch Chief	SES BEIB DRS

COOPERATING UNITS (if any)

RIS, BEIB, DRS

LAB/BRANCH

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The development of a system for transferring the training of Egyptian engineers in equipment repair from NIH to Egypt. The goal is a completely self-sufficient training center in Egypt for recruitment and training of scientific equipment repair personnel. This project is specifically concerned with the development of a 12 week course in basic instrumentation and electronics for scientific equipment.

Z01RS10066-01BEI

Objective: During Phase I of this project, several repair centers were organized and set up in Egypt. The personnel were brought to NIH for training and then sent to the centers. In Phase II, the emphasis will be on developing a facility in Egypt which assumes the training role. At the end of Phase II, the facility should be completely self-sufficient and staffed with Egyptian training personnel.

Significance: At the conclusion of Phase II, the role of NIH in the training process will end and the Egyptian facility must be capable of operating independently.

Proposed Course: A condensed, preliminary version of the training course will be presented in Egypt in October-November of 1981. The purpose is the selection of engineers to return to NIH to be trained in presenting the complete course in Egypt.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10069-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Automated Test Apparatus and Data Handling System for Patient Electrical Safety Program

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Wooten	Electronics Engineer	EEES BEIB DRS
OTHER:	H. Cascio	Electronics Engineer	EEES BEIB DRS
	W. Friauf	Section Chief	EEES BEIB DRS
	H. W. Metz	Chief	RIS BEIB DRS
	W. Connoley	Supervisor	RIS BEIB DRS
	R. Corsey	Electronics Engineer	ACES BEIB DRS
	L. Martin	Programmer	DMB CR
	S. Soroka	Programmer	DMB CR

COOPERATING UNITS (if any)
RIS, DCRT

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronics Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A microprocessor based automatic test set for checking the safety of electrically operated patient care equipment has been designed and built. Test results are stored on cassette tapes which are compatible with the IBM/370 computer. Through discussions with DCRT, a program has been written to input the data from the tapes and file it and manipulate it to provide better documentation and analysis for the safety program.

Z01 RS 10069-02 BEI

Objectives: The objective is to provide an automated test set which can safely and accurately measure the parameters of devices in their operating environment. Also, the objective is to facilitate the handling, storage, and presentation of this data so that the safety of the equipment being tested can be better evaluated and statistical and trend analysis of past and present data can be done.

Methods Employed: Using microprocessor technology, manual input and bar code scanner input can be interfaced to the test set to provide identification of the equipment and annotations on the test itself. A tape transport stores all this data on cassettes.

Significance: By monitoring the results from the safety test data, problems in the safety and everyday operation of the equipment can be detected or even predicted to prevent hazards to the patients.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10071-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes for Cardiac Instrumentation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Chief	MES BEIB DRS
OTHER:	R. Levin	Biomedical Engineer	MES BEIB DRS
	D. Markle	Biomedical Engineer	MES BEIB DRS
	R. Patterson	Senior Investigator	NHLBI

COOPERATING UNITS (if any)

Cardiology Branch, NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The use of miniature fiber optic probes for acute insertion into canine myocardium is being investigated. Measurements of local blood flow and local capillary permeability in the presence of various interventions are contemplated. Practical problems dealing with insertion into tissue, validation of readings, elimination of motion artefacts, and overall characterization of in-vivo performance are of major interest.

Objectives: Perfect and enhance techniques developed for the pH probe (described elsewhere in this years report) utilizing miniature fiber optic probes to measure tissue perfusion and capillary permeability in canine hearts in vivo.

Methods Employed: Utilize miniature fiber optic probes to perform measurements in acute dog experiments. Perform tests to determine practical problems, e.g., breakage, tissue insertion, artefacts, calibration difficulties, elimination of motion artefacts, zero shifts, hysteresis, etc. Develop solutions to above problems using improved probes and signal processing instrumentation.

Significance: At present there are no completely satisfactory techniques for measuring local perfusion, and capillary permeability in-vivo in an "on-line" manner. Perfection of these measurements would represent a great advance in the techniques presently available to experimental cardiologists and other biomedical researchers not only in terms of convenience, but also in terms of opening up many new areas of investigation.

Major Findings and Proposed Course:

(a) Perfusion measurements are feasible, i.e., there is acceptable signal-to-noise ratio. Motion artefacts must be eliminated and an approach is being investigated. Validation using microspheres will be performed once an automatic gain ranging system is implemented so that traces can be reliably obtained. Various flow limited fluorescent markers in addition to fluorescein will be sought. A data acquisition system using a Tektronix 4052 terminal is being developed.

(b) Capillary permeability studies will be investigated after the perfusion techniques has been perfected. Fluorescent labeled compounds of appropriate molecular weight (possibly fluorescein labeled albumin) will be sought and used.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10072-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Clinical Evaluation of Membrane Oxygen Dissociation Curve Analyser

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
	H. Tipton	Mechanical Engineer	ACES BEIB DRS
	D. Lees	Staff Anesthesia	CC NIH

COOPERATING UNITS (if any)
CC - NIH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2	1.5	.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A fully automated, computer controlled method for determining and plotting the entire hemoglobin-oxygen dissociation curve on less than .5 cc of blood has been developed and is being introduced to clinical practice. A micro-computer controls the calibration of the system as well as the initial desaturation and subsequent saturation of the blood specimen.

PHS-6040
(Rev. 2-81)

Methods Employed: Initially the specimen is desaturated by exposure to a CO_2/N_2 mixture. Once the pO_2 falls below 0.5 torr, the computer automatically starts the saturation with a mixture of oxygen and CO_2. Gas is exchanged with the sample in a reaction cell across a silicone rubber membrane which mechanically separates the two phases. The sample solution is contained within an annular region formed by the cylindrical membrane and the sample cavity walls where it is stirred by a thin-walled cupshaped stirrer, magnetically coupled to an outside motor-driven rotor. A conventional polarographic oxygen electrode continuously monitors the partial pressure of oxygen in the sample. The amount of oxygen delivered to the sample is calculated by integrating the diffusion equation and the measured pO_2 gradient across the thin silicone membrane.

Major Findings: The described system appears to be a simple and reliable way of obtaining the hemoglobin-oxygen dissociation curve for clinical applications.

Publications:

Lees, D.E., Schuette, W.H., Thibault, L.E., Kim, Y.D., Tipton, H.E. and MacNamara, M.B.: Computerized Determination of Oxygen Dissociation Curve. Anesthesiology, Vol. 53, No. 3, September 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10073-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981.

TITLE OF PROJECT (80 characters or less)

Secondary Emission Experimental Mass Spectrometer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Associate	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Secondary Emission Mass Spectrometer (SEMS) will be build by Gatan, Inc. and Extranuclear Labs and owned by BEIB Rental Program. It is anticipated that this facility will contribute to research programs in a number of Institutes, specifically NIMH (S. Markey) and NHLBI (H. Fales). The SEMS will have the following features:

(1) Ultra-high Vacuum System - up to 10^{-9} Torr.

(2) Rapid linear motion multi-specimen holder permitting normal and transmission SIMS modes of operation.

(3) Energy analyzed ion gun (.05 - 10 kV) with deflector, pulser, and rastering. The ion gun will allow us to bombard the specimen with ions free of neutrals or by energetic neutrals only.

(4) Quadrupole Ion Storage Device (QUISTOR) and electronics.

(5) Simultaneous CI/EI Ionizer to allow simultaneous spectra in both CI and EI modes of operation.

(6) Secondary Ion Mass Spectrometer in both Reflected (SIMS) and transmission (TSIMS) modes.

(7) Three dimensional mass spectrometry (MS/MS/collision cell double quadrupole system).

(8) Secondary Electron Emission Cell for negative ions studies.

(9) This System will permit us to add later a Sputter Induced Photon Spectrometer to detect the light emitted by sputtering particles. Simultaneous SIPS and SIMS analysis and direct viewing by optical microscope of the target will be available.

The system will feature an MS/MS double quadrupole system. In the last year, the MS/MS technique has been proven to be effective in analyzing mixtures of organic compounds and on many occasions may supplement a GC/MS technique, which is hardly applicable in SIMS. This is a very important feature of the system making it a unique and important for biological applications.

The SEMS will permit us to study secondary emission processes on surfaces under bombardment by electrons, ions, and neutral particles in connection with ionization of organics (compounds of biological interest), to detect sputtered secondary ions and transmitted ions (positive and negative), to detect optical emission of sputtered particles, and to store ions in order to obtain higher sensitivity and selectivity of the mass spectrometric analysis.

The system will be based on Gatan's model 591 SIPS-SIMS Scanning Ion Microbe; various components of the instrument will be modified, adapted and designed to match to one another.

Several components of the system have been already purchased. This includes Extranuclear's plus-SIMS quadrupole mass spectrometer, multi-flange ionization chamber and electron-gun power supply. The ionization chamber was designed this year in cooperation with MDC Manufacturing Co. It is expceted that the instrument will be assembled and tested at Gatan's facility in Pittsburgh and then delivered to NIH sometime this next spring (April-May, 1982).

Thermal Stability in the Ion Source

Other activities under project involved the study of the thermal stability of various organic compounds, including cholesterol, cholestane, cortisole, cortisone, and several epoxides. Styrene Oxide (C_8H_8O) and N-(2,3-Epoxypropyl) phthalamide ($C_{11}H_9NO_3$) were chosen for further investigation as references to determine thermal decomposition in ion sources. Preliminary results suggested that N-(2,3-Epoxypropyl) phthalamide may be used for this purpose in the temperature range 100-300°C in the ion source, by detecting the ratio of the fragment $(M-43)^+$ and M^+(molecular peak). Styrene Oxide may be useful to detect metal chorides formed in the interface between GC and MS.

La B_6 Cathodes Development

The other development is in the field of cold emitters and designing more effective emitters or cathodes for MS ion sources. LaB_6 polycrystalline and single crystal cathodes are developed in cooperation with Kimball Physics for LKB-9000, LKB-2091, MS-9 and Finnigan 4000 instruments. Experimental work is in progress to determine the efficiency and feasibility of applications of these cathodes in mass spectrometry.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10074-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Study of analytical applications of QUISTOR

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Scientist	BEIB DRS
OTHER:	S. Markey	Chemist	LCS NIMH

COOPERATING UNITS (if any)

LCS NIMH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The quadrupole ion store (QUISTOR) or three dimensional ion trap has received little attention among analytical chemists compared to the quadrupole mass filter or two dimensional quadrupole. This is in part due to the fact that QUISTOR primarily has been developed, studied, and used by physicists as partial and total pressure analysers and residual gas analysers and most recently as electronically controlled ion-molecule reaction chambers. Recent works by G. Lawson, R.F. Bonner and R. March employing a three dimensional quadrupole ion trap as an ion source for a mass spectrometer has opened new avenues for the QUISTOR as an analytical tool. The QUISTOR is expected to be more compact, the resolution of the instrument would not be mass dependent as for quadrupoles, and the sensitivity of the device, specifically when detecting single ions, may be improved compared to a quadrupole mass spectrometer combined with a conventional ion source.

The Quadrupole Ion Store was constructed and machined from stainless steel, specifications for the driving electronics have been established, RF-generator modified by Exranuclear Labs. will be used to power the QUISTOR, pulse electronics will consist of a Boxcar Averager and Gated Integrater by EG&G, two pulse generators by HP, X-Y Recorder and Tektronix Oscilloscope.

The budget and financing for QUISTOR electronics have been approved. Gatan, Inc. will incorporate the QUISTOR feature in the SEMS instrument.

Objectives: To develop a QUISTOR-mass spectrometer combination and to study the possible applications in analytical mass spectrometry.

Methods Employed: A three dimensional quadrupole electric field will be used to store ions of interest. This field will be formed by three electrodes of a hyperbolic geometry made of stainless steel, which will consist of two "endcaps" and one central ring. The electron gun will be used to ionize molecules of compounds to be studied. The RF-electric field will be applied to a ring electrode and creation and ejection pulses to the end-caps.

Significance: Development of a three-dimensional ion store and its application in mass spectrometry may result in improvements of detection capabilities of existent instruments and may increase limits of detection of compounds of biological interest.

Proposed Course: Construct the driving electronics and detection system for the QUISTOR. Test the device and study its storage capabilities. Interface the quadrupole ion trap with the gas inlet sysem and the gas chromatograph. Employ different types of electron emitters: hot filaments, field emitters, cold cathodes and find the most suitable emitter for the proposed device. Study the applicability of the QUISTOR to mass spectrometric analysis of drugs and other compounds of biological interest.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10075-02 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Development of a new method for resolving power measurement

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Scientist	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Decachlorobiphenyl and decabromobiphenyl have been analyzed under positive and negative ion chemical ionization and positive ion electron impact conditions for the purpose of using these compounds as references to evaluate the resolving power of mass spectrometers in a wide mass range (M/Z 100-1000). Molecular clusters and some fragments have been detected with different types of mass spectrometers: magnetic sector as well as quadrupoles, including A.E.I. MS-9, LKB-9000, LKB-2091, Finnigan 3200 and Finnigan 4000. The criteria to determine the resolving power have been found based on the measurement of the minima of two adjacent peaks of the molecular cluster of DCB or DBB. Molecular clusters for DCB and DBB were determined theoretically by plotting the individual ions which constitute each profile at the desired resolution using a standard Gaussian distribution of intensities, and then summing the individual ions with the weighting factors derived from the theoretical statistical isotope distribution ratios of carbon, chlorine, and bromine. By comparing the theoretical values of minima vs. resolution with the experimentally found values of minima between the same two adjacent peaks, the resolving power of a given mass spectrometer can be determined. The method

developed here and the reference compounds DCB and DBB will be recommended to manufacturers and users of mass spectrometers as an easy and accurate way to estimate the resolving power of their instruments both for instrument acceptance and as a routine check-out.

Experimental data for the measurement of the resolving power of different types of mass spectrometers have been analyzed. The inlet system to introduce DCB & DBB into the ion source region has been designed in cooperation with Vacuumetrics, Inc. The availability of financing ($52,000) will determine the continuation of this project.

Objectives: To develop a method to measure the resolving power of various types of low resolution mass spectrometers which will be easier, faster and require less effort than the conventional methods.

Methods Employed: Theoretical values of ion abundances for molecular clusters of decachlorobiphenyl and decabromobiphenyl will be used to determine the resolving power of mass spectrometers by comparing them with the experimental values of minima between two adjacent peaks in the molecular cluster.

Major Findings: The calibration curves MIN=f(R) have been found for molecular clusters of DCB(M/Z 498) and DBB(M/Z 944). The comparison between the theoretically derived MIN values and the experimental data show good agreement between observed and calculated values in the resolution range of 150-500 for DCB and 300-900 for DBB. Thus the two compounds cover the useful range of a low resolution mass spectrometer, i.e., 150-900. It also has been found that DBB may be used as a sensitivity test reference for quadrupole mass spectrometers in a high mass range (600-1000). It can be done by comparing intensities of the peaks centered at M/Z 944 and M/Z 784. Their ratio should be about 0.5.

Significance: A simple method to determine the resolving power of mass spectrometers has been developed. The method can be used in all types of mass spectrometers and with different ionization techniques (electron impact, chemical ionization, positive or negative ions, etc.). The method will be beneficialy to all mass spectrometry users and may improve the specifications of the instruments at their acceptance.

Proposed Course: The inlet system for DCB and DBB will be manufactured by Vacuumetrics and evaluated for applications in organic mass spectrometry by NIH.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10078-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Picosecond Spectroscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Smith	Visiting Scientist	BEIB DRS
OTHER:	G. Liesegang	Senior Staff Fellow	LTD NHLBI
	R. Berger	Chief, Sect. of Biophys. Inst	LTD NIHBI
	H. Cascio	Electronics Engineer	BEIB-DRS

COOPERATING UNITS (if any)

LTD NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A picosecond spectrometer has been developed. Single pulses 6 ps in duration are obtained from a neodymium laser at wavelengths of 530 nm and 1.06 u. Simultaneous generation of a white light continuum provides a synchronous monitor source. A vidicon detector has been fully characterized in the pulsed mode of illumination and a technique developed to significantly improve the linearity of response available from a vidicon.

Objectives: To establish a picosecond spectrometer at NIH for the study of the rapid transients occurring in biological molecules. The understanding of these transients is a prime import in elucidating the mode of action of these molecules.

Major Findings: The major emphasis of the picosecond laser spectroscopy project has been directed toward obtaining a complete understanding of the vidicon detector output. The emphasis on this aspect of the project cannot be overstated when it is considered that results obtained otherwise would not stand scrutiny and be qualitative at best. As is outlined below, a significant contribution has been made to the vidicon detector field in this regard.

A Princeton Applied Research Model 1254B SIT Vidicon and 1216 Vidicon controller have been interfaced to a DECLAB-11/MNC computer system. Testing of the OMA revealed a non-linear vidicon output response to the incident pulsed illumination level. It was determined that the factor affecting this non-linear response was the variable recharging rate of the vidicon surface at medium to low light levels. It was also observed that all vidicon scanning parameters alter this response and a careful calibration of the vidicon must be carried out for a particular set of scan parameters, if the OMA is to be used in pulsed spectroscopic applications.

Careful calibration of the vidicon is highly impractical; a prepare-expose-read cathode voltage switching technique has been devised which substantially improves the output linearity of a SIT vidicon in the pulsed illumination mode of operation. This technique now allows quantitative usage of the vidicon in pulsed spectroscopy. This technique is being incorporated into PAR OMA systems as well as numerous spectroscopic systems.

The picosecond laser system is now fully operational. Overlap of the time-dispersed continuum from the echelle and the 530 nm photolysis beam has been established using a carbon disulphide cell and the zero time segment identified. These segments are well resolved on the vidicon. The response of the spectrometer is currently being investigated by studying the known relaxation of the dye azulene; the characteristics of other dyes, not previously studied are being investigated. Electronic synchronization of the firing of laser system at the end of the last prep frame of the vidicon was achieved using an electronic circuit which features opto-isolators. These protect the vidicon controller and data acquisition system from the rapid transients associated with the laser firing and pulse selection. The cyrogenic system has been received and a sample holder has been manufactured for this unit.

Proposed Course: 1) Measurements of the ground state repopulation times of organic dyes will be made to determine the sensitivity of the spectrometer; 2) Application of the spectrometer to membrane dynamics and model heme proteins will be performed to study the role of these effects in cellular function and cooperativity.

Publications:

Smith, P.D., Liesegang, G.W.: Characteristics of a vidicon detector for 3-D spectroscopic applications. Biophys. J. 33, 186a, 1981.

Liesegang, G.W. and Smith, P.D.: Improving vidicon linearity in the pulsed illumination mode. Applied Optics. 20, 2640 (1981)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10079-01

PERIOD COVERED

October 1, 1980 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Optical and Laser Engineering Support

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Smith	Visiting Scientist	BEIB DRS
OTHERS:	R. Hendler	Section Chief	LB NHLBI
	M. Gottlieb		LPB NIAMDD
	R. Nakamura		LPP NIMH
	H. Cascio		BEIB DRS
	T. Clem		BEIB DRS
	R. Bonner		BEIB DRS

COOPERATING UNITS (if any)

LP, NHLBI; LPB-NIAMDD; LPP-NIMH

LAB/BRANCH

BEIB

SECTION

EEE

INSTITUTE AND LOCATION

NIH, DRS, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.35	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Optical support has been provided for the study of very small absorbance changes occurring in turbid cytochrome suspensions and for projection of transient images to measure animal and human response functions. Laser support has been provided for measurement of the phosphorescence resulting from laser excitation of dye molecules embedded in biological membranes. Substantial electronic support has been provided in all cases.

Objectives: To provide assistance in the optical and laser fields for collaborative efforts with investigators requiring this support.

Major Findings: A complete redesign of the light source and optical systems was necessary to reduce the noise in a commercial multi-channel spectrometer (RH). At full gain a peak to peak noise of 15mv is obtained which allows a baseline to be set corresponding to a specific redox state of a cytochrome suspension. By sequentially incrementing the base, full wavelength and time resolution of all the cytochrome redox states is thus obtained.

The shutter of a f1.9 75 mm recording lens was removed and replaced by a fast, electronically activated, two bladed shutter (RN). The modified lens assembly was mounted in a housing suitable for projection of a video CRT image onto a viewing screen. The completed assembly allows an image to be drawn on the CRT screen from computer memory after which the shutter is opened for varied times down to a minimum of 5 ms. A repetition rate of up to 10 frames per second is available.

A dye laser system, using coumarin 6, generating a 1 μ second, 1 Joule pulse at 531 nm has been provided (MG). This light stimulates the dye rosin embedded in a red cell membrane. A detection circuit has been constructed to monitor the resulting phosphorescence, from which the fluidity of the dye in the membrane can be determined. An important feature of the detection circuit is a dynode switching design which reduces the photomultiplier gain during the laser pulse.

Proposed Course: Further development of the red cell membrane experiment to improve the detection unit and to study the effect of various chemicals on membrane function.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10080-01

PERIOD COVERED
October 1, 1980 to September 30, 81

TITLE OF PROJECT (80 characters or less)
Multi-Element Array Detection

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Smith	Visiting Scientist	BEIB DRS
OTHERS:	H. Cascio	Electronic Engineer	BEIB DRS
	I. Levin	Section Chief	LCP NIAMDD
	R. Balaban	Staff Fellow	KE NHLBI
	J. Hofrichter		LCP NIAMDD

COOPERATING UNITS (if any)
LCP NIAMDD; KENHLBI

LAB/BRANCH
BEIB

SECTION
EEE

INSTITUTE AND LOCATION
NIH, DRS, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Multi-element array detectors are being interfaced to varied experimental arrangements to enable simultaneous detection of multiple events with a consequential reduction in experimental time. These projects are similar in nature and are in the initial states of development.

OBJECTIVES: To provide support and expertise in the interfacing of multi-element arrays as experimental detectors. These detectors are becoming increasingly applied, and it is expected the experience gained on these applications will be of use in future collaborations.

Methods Employed: The detectors for all applications are manufactured by Princeton Applied Research. In two cases, (RB, JH) the detectors are vidicon; in the third case, the detector is a multi-element diode array.

An electronic circuit was designed and constructed to allow the electron beam reading voltage to be switched after the completion of the preparation frames. This significantly improves the linearty of response of the vidicon under pulse illumination conditions; for a 1.5V increment in voltage a correlation of fit to a straight line of 0.99 is obtained for the vidicon response. This circuit has been incorporated in the 1252 vidicon (JH).

A model 1254 SIT vidicon is to be used as the detector in fluorescence microscopy (RB). This vidicon will be interfaced directly to a Digital Equipment Corporation MNC11 computer which will be used for control of the vidicon and for data gathering. An electronic circuit is being designed to provide a standard video signal from the 1254 suitable for presentation to commercial monitor sets and video tape recorders. A Spectra-Physics model 164 krypton laser has been aligned for excitation of the fluorescence.

A model 1452 linear diode array detector is to be interfaced as a detector for Raman studies (IL). In this instance, an intelligent controller, which will direct the setting of the experiment sample temperature in a pre-programmed sequence and will direct the date gathering by the diode array, has been designed and is being constructed.

Proposed Course: To finish the design and testing of the various circuits before incorporating them into the experimental apparatus for evaluation. To write the programming necessary for control of the detector and for data gathering. To provide support for future usage of multi-element arrays.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10081-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Photo-Irradiation of Cancer Cells

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Smith	Visiting Scientist	BEIB DRS
OTHERS:	P. Ebert	Research Chemist	VB NCI
	R. Bonner		BEIB DRS
	D. Tschudy	Senior Investigator	MET NCI
	J. Costa	Staff Physician	CNB NIMH

COOPERATING UNITS (if any)

VB-NCI;MET-NCI;CNB-NIMH

LAB/BRANCH

BEIB

SECTION

EEE

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The effect of various wavelengths of light have been studied for the relative effectiveness in killing leukemic L1210 cancer cells incubated with hematoporphyrin. Investigations were also performed to determine the enhancement of this light effect after introduction of enhancers into the medium which stimulate hematoporphyrin uptake by the L1210 cells.

Z01 RS 10081-01 BEI

Objectives: To establish dose levels of the illuminating light required to produce various reductions in viable cell population: To determine the relative merits of enhancers which stimulate hematoporphyrin uptake by L1210 cells in photo induced killing.

Methods Employed: A lantern slide projector was modified to provide an illuminated 2" by 2" area suitable for exposing the flasks containing the L1210 cells. Provision was made for insertion of interference filters at specific wavelengths corresponding to absorption peaks for hematoporphyrin (397 nm, 531 nm, 566 nm, 621 nm, and 636 nm) and also for accommodating heat rejection filters. Exposure levels of the illuminating light were measured using a commercial (EG & G) radiometer. Typical levels are 3 mw/cm^2. Exposure times ranged from less than one minute to 30 minutes.

Major Findings: The in vitro studies performed have demonstrated that L1210 cells are killed by light if they are previously incubated in the presence of hematoporphyrin. Plots of leg cell count vs. time show a linear increase in time for the non-illuminated control and a fall in cell count for two days followed by subsequent growth in parallel with the control for the illuminated cells. For lethal doses of illumination this growth does not resume. The effectiveness of the killing was determined by measuring the ratio of the curves after resumption of growth. 636 nm has been found to be almost non-effective in killing L1210 cells, with 397 nm, 531 nm, and 621 nm being the most effective: experiments are underway to establish the relative effectiveness of these wavelengths for future in vivo work where other factors complicate the selection of the most effective wavelength. A quantitative measure of the enhancement attained with succinyl acetone, dibucaine, and chloraquine has not yet been made though it has been observed that these agents reduce the illumination period for equivalent killing.

Significance: Phototherapy is becoming a course of treatment for certain types of cancer. By establishing wavelength criteria and enhancing the light effect, improved photo-therapy will be made possible.

Proposed Course: To extend the in vitro studies to in vivo work. Initial studies will be performed on mice.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10082-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Protein Sequencer Modification

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Lutz	Chemical Engineer	BEIB DRS
OTHER:	E. Appella	Chief	LCB NCI
	J. Martin	Medical Equipment Repairer	BEIB DRS
	K. Yonaha	Guest Worker	DBBP BB

COOPERATING UNITS (if any)

LCB/NCI, DBBP/BB

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	.75	.25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Proteins serve an incredible variety of biological functions which are determined indirectly by the amino acid sequence in the protein. The most effective single method for sequence determination is the degradation technique of Edman, which is performed by an automated instrument manufactured by Beckman. By a repetitive sequence of processes, amino acids are chemically cleaved one by one from the N-terminal end of a large protein or polypeptide. Recently, proteins of considerable interest are being isolated only in minute quantities, too small for accurate determination on available automated instruments. The goal of our project is to discover improvements to the present protein sequencing methodology that will allow for "microsequencing." The present emphasis is on improvements in the design of the automated sequencer. The three main features in the design that require improvements are (1) reagent and solvent delivery valve mechanism, (2) vacuum system, (3) automatic conversion of cleaved amino acid to a more stable phenylthiohydantoin derivative for analysis.

Objectives: To discover improvements to the present protein sequence methodology that will allow for "microsequencing." Three areas are involved in the overall improvement of the present Edman degradation method: (1) sample purification and preparation, (2) reagent and solvent purification, (3) more sensitive analytical techniques, and (4) modification in the design of the automated sequencer. Ultimately, new approaches will be investigated for microsequencing of proteins such as solid phase, gas phase, and membrane reaction and separation techniques.

Methods Employed: The present emphasis is on modifications to the Beckman sequencer in three specific areas. (1) Reagent and Solvent Delivery Valves: A new, more reliable and precise valve has been designed for delivery of solvents and reagents to the reaction chamber (spinning cup). It is a specially designed manifold system with zero hold-up volume. All parts in contact with chemicals are made of teflon and therefore are inert. The new valve replaces a cumbersome system of valves in the old machine. (2) Vacuum System: High and low vacuum are regulated by two Leybold-Heraus stainless steel vacuum valves connected in series. These valves are connected to a rotary vane vacuum pump through a liquid nitrogen cold trap that allows vacuum down to 1 micron thus reducing backflux into the reactor of vapors from volatile solvents or reagents between run cycles. Vacuum pump oil stays cleaner longer. (3) Reaction Chamber: The reaction chamber has been redesigned to contain fewer O-ring seals thus reducing leakages of oxygen into the system which is detrimental to the chemical reaction scheme. (4) Automatic Converter: An automatic converter has been installed on the sequencer. This all glass unit converts the cleaved anilinothiazolinone amino acid derivatives to a more stable phenylthiohydantoin for eventual analysis and identification by high pressure liquid chromotography.

Significance: Proteins of significant scientific interest are often available only in sub-nanomole quantities. Progress in the elucidation of the primary structure of these proteins can be achieved by a number of improvements in techniques for amino acid sequence analysis. The first advances are being made now by employing technical improvements of the Beckman liquid-phase sequencer, including addition of an automated conversion device. New techniques now being tested may further improve protein sequence methodology, e.g. gas-phase instruments.

Proposed Course: (1) install new delivery valve unit on old Beckman 890C; (2) install new autoconverter; (3) incorporate improved vacuum system with liquid N_2 cold trap in system; (4) test assembled unit on standard protein (myoglobin); (5) check for lower limit of sensitivity of new unit (down to 1 nanomole sample); (6) consider improved design for solid-phase sequencing system; (7) study any new, proposed methods of sequence analysis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10083-01

PERIOD COVERED

August 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Study of Oxygen Transport in Peruvian High Altitude Natives

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.C. Gibson	Electrical Engineer	BEIB,DRS
OTHER:	R.M. Winslow	M.D.	CDC
	H.G. Klein	M.D.	Bloodbank, CC
	S. Rosen		Bloodbank, CC
	N. Statham		CDC
	C.M. Monge	M.D.	U. Cayetano Heredia Lima, Peru
	E. Monge	M.D.	U. Cayetano Heredia Lima Peru

COOPERATING UNITS (if any)

lood Bank, Clinical Center Center for Disease Control, Atlanta, Georgia

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Electrical and Electronic Engineering Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A field trip to determine the work capacity of high altitude natives (14,850 ft) suffering from Monge's disease before and after phlebotomy. Using a computer controlled exercise stress test, several high altitude natives were tested before and after massive phlebotomy. Enough red cells were removed and replaced with albumin to lower their hemocrit to 50-52%. This usually meant that three liters of red cells were removed. In all cases, the improvement in performance was dramatic ranging from 50%-150% increase in work output.

Objectives: To see whether or not massive phlebotomy is of benefit to the high altitude native suffering from Monge's disease.

Methods: A breath by breath computer controlled exercise test was used, coupled with various opti-sats and catheters in place to measure arterial and veinous oxygen saturation. A Heamonetics cell separator was used for the phlebotomy.

Significance: Phlebotomized natives could work harder and longer than they could before. If this method works over a long period of time it will benefit the Peruvian people and economy directly.

Proposed Course: Another trip is planned for January 1982 to study the previous patients again, and to phlebotomize another series of patients, looking carefully at renal function and measuring red cell mass.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10084-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Instrumentation for Microcalorimetry Data Acquisition and Correction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.C. Gibson	Electronics Engineer	BEIB, DRS
OTHER:	R. L. Berger	Physicist	LTD, NHLBI
	C. Mudd	Mechanical Engineer	BEIB, DRS

COOPERATING UNITS (if any)

Laboratory for Technical Development, NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Electrical and Engineering Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A microcomputer based data collection and reduction system has been implemented to calculate the total heat output and power vs. time of a batch calorimeter with provisions for plotting the data.

Z01 RS 10084-01 BEI

Objectives: To provide a data collection system capable of correcting the input data so that a true heat of reaction and power curve can be realized from a batch calorimeter.

Methods: A programmable gain 16 bit A/D converter has been utilized to obtain the needed accuracy for a finite element scheme to do the data correction.

Significance: The data collection and reduction scheme allows detection of 5×10^{-9} calories for enzyme reactions thus allowing many more reactions to be studied.

Proposed Course: To average the incoming data and extend the system to include a differential-ph-thermal titration apparatus.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10085-01

PERIOD COVERED

July 26, 1981 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Buckling Modes of Growing Venules

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: A.M. Waxman — Physical Scientist — BEIB, DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.05	0.05	0.00

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A physical model has been developed to describe the mechanics of growing blood vessels. The blood vessel is treated as a growing elastic shell imbedded in a surrounding viscous fluid (the tissue). As the vessel grows, it buckles in any of three possible modes, varicose, sinuous, or helical, and with a particular wavelength in each case. Solutions of the governing equations for the geometry and mechanical force balance are currently being sought for the sinuous and helical modes. This work is an extension of previous work on the axisymmetric, varicose mode.

Objectives: The short term objective is to develop confidence in the conceptual model proposed here for the stimulated growth of small blood vessels. Satisfactory comparison between theoretically predicted wavelengths for the various buckling modes with measurements made from experiments on tumor angiogenesis would lend credence to the ideas set forth in earlier work.

Methods Employed: Analytical methods are used to solve the equations governing the physical model. The nonlinear partial differential equations are solved exactly for the case of a uniformly dilating vessel. The buckling sets in as an instability of the slowly dilating state. The dominant wavelengths are extrated by a perturbation analysis for each separate mode.

Significance: With regard to tumor angiogenesis, the model gives us a framework which helps explain the presence of tortuous and focally dilated blood vessels in the vicinity of a tumor inplant. It seems that new capillaries sprout in the vicinity of the wavecrests associated with buckling and thus, the buckling of preexisting vessels is intimately related to the vascularization process of the tumor itself.

Proposed Course: If the buckling theory continues to yield satisfactory predictions for the wavelengths of the various modes, it can then be utilized to explore the sprouting phenomenon. By considering the reaction-diffusion dynamics of growth promoters and inhibitors on buckled surfaces, we hope to identify sprouting sites as regions of enhanced promoter concentration on the vessel surface.

Publications:

Waxman, A.M.: Blood vessel growth as a problem in morphogenesis - A physical theory. Microvascular Research (in press).

Waxman, A.M.: A continuum approach to blood vessel growth-axisymmetric elastic structures. J. Theoretical Biology (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10086-01

PERIOD COVERED

July 26, 1981 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Theory of Lateral Diffusion in Cell Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: A.M. Waxman	Physical Scientist	BEIB, DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.05	0.05	0.00

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Lateral diffusion of proteins in cell membranes is treated as a problem in Brownian motion through a two-dimensional viscous fluid membrane with curvature and of finite area. Analogous to the Stokes-Einstein relation for diffusion through a viscous bulk fluid, we seek to relate the diffusion constant of a protein in a membrane to the rheological and geometrical properties of the membrane as well as to the size of the protein molecule.

Objectives: Our first objective is to calculate the hydrodynamic drag force exerted on a protein moving through a fluid membrane of finite area which possesses finite curvature as well. This drag force may then be utilized in a Langevin-type approach to Brownian motion in such a membrane.

Significance: We hope to develop a physical understanding of lateral diffusion in cell membranes. Diseased states of the membrane will affect its rheology as well as its shape, and this should reflect itself in altered diffusion rates of proteins. This, in turn, will influence the overall performance of the cell.

Proposed Course: At first, the membrane is being treated as a two-dimensional viscous fluid. In the future we hope to consider more realistic viscoelatic fluid models for the cell membrane.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10087-01

PERIOD COVERED

July 26, 1981 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Mechanics of Red Blood Cells in Flow

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A.M. Waxman	Physical Scientist	BEIB, DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The red blood cell is modeled as a fluid droplet surrounded by a viscoelastic fluid membrane which possesses a bending resistance. The resting shape of the cell is taken to be a biconcave disk. When the cell is immersed in a shear flow, it deforms in shape and sets up an internal circulation as well as a membrane flow. We seek to calculate such shapes from mechanical considerations, and relate shape and flow to membrane rheology.

Objectives: We seek to relate red cell shape and deformability to membrane rheology via these hydrodynamic calculations. Then, by comparing the calculated shapes to those observed experimentally, we hope to determine the rheological constants which characterize the mechanical properties of the lipid bilayer-spectrin composite which forms the membrane.

Methods Employed: The formalism developed by Waxman to describe the mechanics of deforming surface continua shall be utilized here. This theory of the kinematics, dynamics, and rheology of evolving surface phases enables us to describe the membrane flow for a deforming cell. The internal flow shall be modeled as an incompressible viscous fluid. The governing equations must be solved numerically.

Significance: Various diseases states are characterized by altered mechanical properties of the erythrocyte membrane. This manifests itself in altered deformability, and this in turn affects the flow properties of blood (as a suspension of red cells). Thus, it is important to understand the mechanics of the membrane itself and how it relates to red cell deformability.

Publications:

Waxman, A.M.: Dynamics of a couple-stress fluid membrane. J. Fluid Mechanics (in press).

Waxman, A.M.: A corotational time-derivative for surface tensors, constitutive relations, and a new measure of bending strain. J. Non-Newtonian Fluid Mechanics (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10088-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Multimode R5232-C Data Switch

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: C.C. Gibson	Electrical Engineer	BEIB, DRS

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Electrical and Electronic Engineering Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

With the advent of smart instrumentation, methods are needed to transfer the data from the instrument to a large computer for analysis. This particular device allows a large coulter counter to transfer its data to either an NIH 7000 terminal or to the DEC-10 computer without cable switching.

Objective: To transfer data from a coulter counter to the DEC-10 computer.

Methods: This switch utilizes a diode OR-Gate so that an interactive terminal can stay on line to the computer at the same time the Coulter counter is on line and transfering data.

Significance: This device enabled the researcher to process twice as many samples per day.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10089-01

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Non-invasive Hemoglobin Measurement

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.C. Gibson	Electronics Engineer	BEIB, DRS
OTHER:	H.G. Klein	M.D.	Blood Bank, C.C.
	S. Rosen		Blood Bank, C.C.
	V. Weber	R.N.	Blood Bank, C.C.

COOPERATING UNITS (if any)

Blood Bank, Clinical Center

LAB/BRANCH
Biomedical Engineering and Instrumentation .

SECTION
Electrical and Electronic Engineering Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.4	0.6

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In the treatment of thalassemia, iron poisoning from frequent transfusions is the primary cause of death. If neocytes only are transfused then the frequency of transfusions is cut by half. To collect neocytes, a method was needed to continuously monitor the hemoglobin concentration of the output of an IBM continuous flow cell separator. A device was designed and built that continuously measures hemoglobin concentration non-invasively. The sensor head fits over the output tube and uses optical methods to measure the hemoglobin concentration. The device will measure from 0-12g% concentration with less than .3g% error.

Objectives: To measure hemoglobin concentration from 1.g% to 5.0g% non-invasively and continuously.

Methods Used: Optical density measurements are done using optical feedback through the solution being measured. The device is slipped over the output tube of the IBM continuous flow cell separator making it completely non-invasive.

Significance: This device aids in the collection of neocytes and allows the operator of the cell separator to keep the interface essentially constant.

Proposed Course: To more fully calibrate the instrument and prepare a publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10090-01

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Computer-controlled Fermentation System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.R. Clem, Sr.	Electronic Engineer	EEES,BEIB, DRS
OTHER:	Yossi Shiloach	Chief, Power Plant Unit	LNE NIADDK

COOPERATING UNITS (if any)
LNE, NIADDK

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A computer controlled fermentation system is being developed for monitoring and controlling the fermentation process. The system will be assembled using primarily commercial instruments interconnected via the IEEE-488 GPIB. This approach will allow scaling the process to different size vats with a minimum of changes required.

Z01 RS 10090-01 BEI

Objectives: Design and implement an instrumentation and control system to allow monitoring and control of the fermentation process in any of several fermentation vats.

Methods Employed: The first system to be assembled will consist of some instruments which were already in use in the pilot plant and some instruments which were purchased specifically for this project, all connected to an inexpensive desk-top computer. The computer is programmible in BASIC, which allows the experimenter to easily produce the controlling and monitoring programs. Most all interconnections to the computer will be via the IEEE-488 GPIB.

Significance: Computer monitoring and controlling of the fermentation process will produce several significant advantages over the present methods. By using the computer to make decisions based on what is occuring in the fermentation process, parameters can automatically be altered to produce either an increased yield of a desired product or a more pure form of the product. The computer can also perform some of the "housekeeping" tasks associated with running a fermentation process that would normally require an operator.

Proposed Course: To assemble a basic system to begin controlling and monitoring a fermentation process to determine where further effort or refinement is necessary.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10091-01

PERIOD COVERED

October 1, 1980 to September 31, 1981

TITLE OF PROJECT (80 characters or less)

Mechanics of Red Blood Cell Membrane

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.R. Markle	Biomedical Engineer	BEIB, DRS

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.1	.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

a micromanipulation system consisting of an inverted microscope, two micro manipulators and video equipment necessary for the recording and analysis of data has recently been acquired. This system will be used to investigate the intrinsic material properties of red cell membrane and large lipid vesicles using micropipette aspiration and flow channel techniques.

Methods: Presently both micropipette aspiration and slow channel techniques are being developed and will be used in the above studies. However, the system is flexible and can be readily adopted to the needs of any specific experiment.

Proposed Course: Initially the system will be used to investigate the intrinsic material properties of red cell membrane in diseased states. At the present time red blood cells obtained from diabetics are of primary interest. However, red cells from patients with sickle cell anemia and muscular dystrophy etc. are also of interest and will be studied. Other uses of this system may include studies of cell lysis during the freezing and thawing process used in blood storage, measurement of the affinity of red blood cell membranes for particle surfaces, and measurements of the mechanical properties of both pure and multiphase vesicle systems.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10092-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Low Duty Cycle, Pulsed Electromagnetic Blood Flowmeter

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.P. Mudd	Biomedical Engineer	MES, BEIB, DRS
	R. Patterson	Senior Investigator	Cardiology, NHLBI

COOPERATING UNITS (if any)

Cardiology Branch, NHLBI

LAB/BRANCH

BEIB

SECTION

MES

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To design, construct, and evaluate a prototype of a low duty cycle pulsed electromagnetic blood flometer. The design will use an excitation scheme which will simplify probe construction and also increase reliability.

Z01 RS 10092-01 BEI

Objective: By using a pulsed excitation scheme, it is possible to eliminate the quadrature voltage problem. Without the quadrature signal, we can simplify the probe design and thus produce a more reliable instrument.

Significance: If we use A.C. excitation in an electromagnetic flowmeter, a quadrature voltage, E_q is created which is generally orders of magnitude greater in amplitude than the flow-induced signal. In practice, to reduce E_q, the probes are partially assembled and when excited, the electrode leads are moved to reduce E_q. The probes are then encapsulated. Because of this procedure, the probe cost is high, $500/unit, and any subsequent change in the capacitive or inductive voltages will upset the nulled condition and increase E_q thus rendering the probe useless. If the above scheme can be implemented, this problem will be eliminated.

Proposed Course: (1) Design the signal amplifier and associated circuits; (2) Design a pulse amplifier to drive the probes; (3) Redesign the probe to ensure that the magnetic field is constant across the lumen.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10094-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Removal of Atherosclerotic Plaque from Arterial Walls Using A Special Purpose Catheter

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Chief	MES BEIB DRS
OTHER:	K. Kent	Chief	CDS CB NHLBI

COOPERATING UNITS (if any)

Cardiovascular Diagnosis Section, Cardiology Branch, NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A variety of concepts will be investigated to determine the feasibility of developing a special purpose catheter to removed arterial plaque from coronary vessels. Use of lasers, ultrasonics, and mechanical means will be evaluated as appropriate.

Objective: To conceive and determine the feasibility of various techniques of removal of plaque from arterial wall.

Significance: The development of a technique for removal of plaque via a catheter would aleviate the need for open chest surgery in some cases, and allow treatment in other cases where such surgery cannot be done. This would be of great importance in the treatment of coronary artery disease.

Proposed Course: a) Conceive of and evaluate concepts for plaque removal; where appropriate perform critical experiments, b) develop a miniature fiber optic imaging catheter to visually examine coronary vessels.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10095-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Multiple Probe pH Measurement System for Canine Myocardium

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. Markle	Biomedical Engineer	MES BEIB DRS
OTHER:	D. McGuire	Mathematician	MES BEIB DRS
	S. Goldstein	Chief	MES BEIB DRS
	R. Patterson	Senior Investigator	NHLBI

COOPERATING UNITS (if any)
Cardiology Branch, NHLBI

LAB/BRANCH
Biomedical Enginering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

For the past several years, considerable effort has been expended on the development of a miniature fiber optic pH probe for physiological use. With the first generation of probes and support equipment the feasibility of optically measuring pH via a pH sensitive dye was demonstrated and many subtleties associated with the probe construction and use made apparent. With this knowledge and experience and improved probe and multichannel support system has been designed and constructed and is presently being used to measure pH in the wall of beating canine hearts.

Objectives: To provide a pH probe which was rugged, easily and atriumatically inserted into a beating heart, free from motion artifacts, quick to respond to pH changes and able to resolve pH with a spatial resolution of approximately 0.5mm. Furthermore the support system was required to provide continuous data (visual and hard copy) for each of five probes.

Methods Employed: The probe was redesigned to fit into a 25 gauge (0.5mm diameter) stainless steel needle by reducing the diameters of the optical fibers to 0.075mm and the inside diameter of the semi-permeable membrane is provided by two slots machined in the needle wall and a transverse hole 0.368 mm in diameter. This design increased the probes' durability and eliminated all motion artifacts. In addition, the smaller probe dimensions reduced the insertion trauma and decreased the 90% step-response time from approximately 90 to 30 seconds. The spatial resolution of the probe was increased by concurrently reducing the dye column length to 0.12 mm and terminating the column with a reflective surface. The mirror surface is required to avoid excessive light loss through the end of the dye column.

Significance: At the present time this is the only system available to measure tissue pH in-vivo and on line. Such information is of use to experimental cardiologists interested in evaluating drugs which affect tissue perfusion, obstetricians interested in monitoring fetal scalp pH and biomedical researchers in general.

Proposed Course: To further improve the reliability and ease of operation of the system and to reduce its size and cost.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10096-01

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Light Scattering Method for Evaluation of Platelets

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.F. Bonner	Physicist	BEIB DRS
OTHER:	P. Smith	Visiting Scientist	BEIB DRS
	J. Fratantoni	Dir. Blood Bank Products	BB FDA
	B. Poindexter	Biologist	BB FDA

COOPERATING UNITS (if any)
Bureau of Biologics, FDA

LAB/BRANCH
Biomedical Engineering and Instrumentation Branch

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Assessment of the functional status of platelets for transfusion is confounded by the inherent complexity of the cell, as well as the intricate requirements of sample preparation. A correlation between discoid shape and functional integrity of the platelet has been established. We have developed a simple prototype instrument for measuring the fraction of discoid platelets quantitatively in standard blood bank platelet concentrate units within their bags. Our instrument detects the light scattered (633nm) between 5 and 6 degrees of the forward beam. The plasma may be made to flow perpendicular to the incident beam through a narrow parallel plate gap. Discs orient face on to the beam and consequently scatter light through a smaller angle than the randomly oriented platelet. The change in light scattered at 5 degrees for the flowing (oriented) platelets from that of resting (randomly oriented) platelets is a quantitative measure of the fraction of discoid platelets. This measurement has been correlated with other measures of platelet function.

Rigorous light scattering theory has been applied to this problem in order to provide a quantitiative method for the wide range of blood bank samples.

Objectives: Develop an optical method to evaluate platelets in standard blood bank platelet concentrates.

Methods: Angular light scattering studies on platelet suspensions and from blood bank samples in PVC bags formed the basis of a prototype low-angle light scattering instrument. Measurement on a large number of platelet concentrates in parallel with biochemical and visual grading provided a basis for the evaluation of the light scattering method. Light scattering theory is being applied to this data base in order to understand the effects of the platelet number density and fraction that are discs on the measured values. This theoretical understanding will direct modifications of the instrument in order to provide best quantitative assessment for the wide range of platelet concentrates produced by blood banks.

Major Findings: The difference in scattering at 5 degrees between oriented and unoriented platelet suspensions provides a quantitative assessment of platelet function as determined by parallel methods. The prototype instrument allows the rapid (1 minute) assessment directly on the platelet concentrate bag without the possibility of contamination.

Multiple scattering theory predicts the observed dependence on platelet number density and sample thickness and indicates that a 5 degree measurement for a 3mm sample path is optimum for the observed range of platelet densities (0.6 to $2.0 \cdot 10^6$ per mm^3).

The relaxation rate of platelet orientation also provides a measure of platelet asymmetry, which however, is strongly dependent on the normal variations in plasma viscosity.

Significance: A rapid, noninvasive quantitative optical grading of platelet concentrates would provide optimal utilization of the blood bank product for transfusion. Additionally it would allow continuous quality control of the preparation and storage of the platelet concentrates at blood banks and hospitals.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10097-01

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Mechanics of the Left Ventricle

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.S. Chadwick	Biomedical Engineer	BEIB DRS
OTHER:	R. Patterson	Senior Investigator	Cardiology NHLBI

COOPERATING UNITS (if any)
NHLBI-Cardiology Branch

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A theoretical analysis of the mechanics of the left ventricle has been undertaken in which the myocardium is modeled as a fluid-fiber continuum. The passive and active length-tension relations of papillary muscle are applied to the three-dimensional architecture of the myocardium. The anisotropic elastic behavior is crucial to understanding the contractility of the myocardium, the development of systolic pressure, pumping of blood out of the ventricular chamber, and the flow of blood in the myocardium itself.

Z01 RS 10097-01 BEI

Objectives: To develop a quantitative theory which describes the mechanical events in the left ventricle throughout the cardiac cycle.

Methods Employed: The myocardium is idealized as a continuum of muscle fibers imbedded in an incompressible fluid. The fiber direction field measured by Streeter is an essential part of the theory in which a pressure field develops in the tissue to support the tensile streses which act along the fiber directions. The passive and active states of the muscle fibers are characterized by the known tension-sarcomere length relations for papillary muscle. Boundary value problems are formulated for the various phases of the cardiac cycle.

Major Findings: Solutions have been obtained so far for the passive diastolic filling phase and then subsequent isovolumic contraction in a finite cylindrical model of the left ventricle. Some interesting results already emerge from the analyses, e.g. the isometric contraction in a muscle preparation is not equivalent to the isovolumic contraction phase of the heart. Also the physiological distribution of fiber angles appears to maximize the development of systolic pressure.

Significance: Further development of the theory will help in the understanding of ventricular hypertrophy, and help to quantify contractility which is an important index in the assessment myocardial ischemia.

Proposed Course: The analysis will be extended to complete the cardiac cycle, a more realistic ventricular geometry will be considered, and an analysis of myocardial blood flow will be undertaken.

Publications:

Chadwick, R.S.: The Myocardium as a Fluid-Fiber Continuum: Passive Equilibrium Configuration. 1981 Advances in Bioengineering, ASME, (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10098-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

CO_2 Laser Vitrectomy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	MES BEIB DRS
	R. Bonner	EEES BEIB DRS
OTHER:	S. Meyers	NEI

COOPERATING UNITS (if any)

MES, EEES

LAB/BRANCH

BEIB

SECTION

MES

INSTITUTE AND LOCATION

NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.45	.4	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A pulsed CO_2 laser vitrectomy system is being developed for NEI. It is expected that the pulsed laser energy will locally cut vitreous bands without creating transient tension on their vertical attachments. Additionally the infrared pulse will be absorbed within 100 μm of the intraocular probe without appreciable thermal diffusion (allowing access to bands lying 1-2 mm above the retina). The laser has been set up and tested in an animal surgery room. An articulated arm and waveguide intraocular probe are being constructed. An alternate fiber optic delivery system supplied by a commercial source is being tested.

Objective: To develop an intraocular CO_2 laser surgical instrument capable of cutting vitreous bands without damage to nearby retina.

Methods Employed: Construction of the laser system and testing it on living animals with vitreous bands (rabbits, monkeys). Construction to date includes adaptation of commercial CO_2 laser to two prototype delivery systems: 1) articulated arm with protected silver mirrors and lens containing tapered gold surface waveguide (1mm diameter for intraocular tip) with diamond window; 2) thallium bromoiodide fiber optic delivery system. Animal experiments to date suggest laser system with $\geq 25\%$ efficiency probe (fiber optic) are sufficient to cut vitreous bands without short term retinal damage at $>$ 2mm from probe. The relative efficacy of the two prototype delivery systems will be further tested. Testing of components of prototype 1) articulated arm system suggest an efficiency of $>25\%$ when a focusing lens is used.

Significance: The present laser system with one or the other delivery system appears to offer a viable alternative to current mechanical vitrectomy cutters.

Proposed Course: Further animal testing of the requirements, methodology, and hazards of the laser vitrectomy cutter are being pursued. Accompanying modification of two prototype delivery systems will provide the vitreous surgeon with the most versatile and useful instrument for evaluation of efficacy in clinical trials.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10099-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Cochlear Mechanics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. S. Chadwick Biomedical Engineer BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation Branch

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is concerned with a theoretical analysis of the propagation of mechanical waves in the cochlea. These waves result from the input action of the stapes footplate and the subsequent interaction of the basilar membrane with the cochlear fluids. The stereocilia of the hair cells deform due to the wave motion and convert information contained in the waveform to electrical impulses. A quantitative understanding of the wave patterns and the mechanical factors affecting them is essential for an understanding of the hearing process. The influence of cochlear geometry, fluid and membrane viscosity, and elastic coupling in the basilar membrane are being studied.

Objectives: To calculate the velocity and pressure fields in the cochlear fluids, and the displacement field of the basilar membrane, in response to various types of physiological input sounds.

Methods Employed: The appropriate equations of fluid and solid mechanics are written in linearized form to obtain the basic hydroelastic boundary value problem. This problem is then solved using a variety of methods of asymptotic analysis. The basic small parameter is the slenderness of the cochlear geometry. Low and high frequency limits are studies, as well as the effects of elastic anisotrophy of the basilar membrane.

Significance: The ear has the ability to distinguish different tones with high sensitivity. One outstanding question in auditory physiology is whether the main auditory analysis is performed mechanically or by neural means. Theoretical calculations of the type being done in ths project will help to answer this question.

Proposed Course: A study of the micromechanics of Organ of Corti is planned, as well as the electro-mechanics of the hair cell transduction process.

Publications:

Chadwick, R.S.: Studies in Cochlear Mechanics. Lecture Notes in Biomathematics, in Proceedings of NSF-CBMS Regional Conference on Mathematical Modeling of the Hearing Process 1980, Springer-Verlag, NY, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10100-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Mechanics of Muscle Contraction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. S. Chadwick	Biomedical Engineer	BEIB DRS
OTHER:	R.J. Podolsky	Chief	LPB NIAMDD

COOPERATING UNITS (if any)
NIAMDD - Laboratory of Physical Biology

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An outstanding unanswered question in muscle physiology is concerned with the details of the molecular mechanisms involved in the generation of force. Physiological experiments on striated muscle aimed at obtaining information at the cross bridge level are often complicated by unwanted effects which make interpretation difficult. Some of these are nonuniform sarcomere lengths, end effects due to tendons and clamping, dispersion of fiber lengths, nonalignment of striations across the muscle cross section, and mechanical wave propagation effects. A continuum theory incorporating sarcomere interactions would be very useful in interpreting physiological data.

Objectives: To develop a continuum theory of striated muscle contraction incorporating sarcomere interactions for the resting, active, and rigor physiological states.

Methods Employed: As a first step, a one-dimensional theory will be developed which will incorporate the three distinct length scales which appear in the mechanical descirption of muscle contraction. Events at the cross bridge level occur on a scale of nanometers, those at the sarcomere level occur on a scale of microns, while the total length of the fiber is typically several millimeters. A fiber is composed of about 10^4 sarcomeres in series. The equations of motion and energy of a sarcomere involve the statistical mechanics and biochemistry of the cross bridge interactions and the interactions with nearest neighbor sarcomeres. The continuum limit of the equations of the chain yields a system of partial differential equations to be studied.

Significance: Mathematical solutions of the boundary value problems can simulate and lead to a better understanding of physiological experiments on muscle contraction.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10101-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Cryopreservation of Neural Tissue

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L.Levin	Mechanical Engineer	BEIB DRS
OTHER:	D.C.Klein	Senior Investigator	LDN NICHHD

COOPERATING UNITS (if any)
LDN-MICHHD

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.02		

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop an optimum freeze-thaw protocol for neural tissue in order to permit its long term preservation.

PHS-6040
(Rev. 2-81)

Objectives: To develop optimum techniques for the long term cryopreservation of neural tissue.

Methods Employed: An experimental study of the response of neural tissue to freezing and thawing at specific rates will be conducted utilizing a controlled rate LN_2-microwave freeze-thaw device previously developed.

Significance: The long term cryopreservation of neural tissue will greatly facilitate analyses of neurological activity and the development of neural tissue transplant techniques.

Proposed Course: A comprehensive experimental study of the optimum cryopreservation protocol for neural tissue will be investigated using a controlled-rate LN_2-microwave freeze-thaw device.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10102-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Osmotic Behavior of Perfused Tissues and Organs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L.Levin	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.15		

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the osmotic behavior of perfused tissues and organs during the introduction and removal of cryoprotective agents (CPAs) from both an analytical and an experimental point of view. Comparison of theoretical predictions of organ behavior during CPA introduction and removal based upon a newly developed non steady state mass transfer model with experimental observations of the responses of perfused organs to changes in the composition of their perfusates will hopefully facilitate the development of optimum CPA introduction and removal protocols.

Objectives:

(1) To develop a non-steady state mass transfer model of the osmotic response of perfused tissue and organs to the introduction and removal of cryoprotective agents experimentally.

(2) To experimentally observe the osmotic response (i.e., changes in weight, vascular resistance and effluent composition) of isolated perfused organs to the introduction and removal of cryoprotective agents.

(3) To correlate our analytical and experimental findings and deduce the rate-limiting transport parameters.

(4) To develop optimum CPA introduction/removal protocols.

Methods Employed:

(1) Mathematical modeling and data analysis will be accomplished through the use of NIH's DEC-10 computing system and associated computer graphics facility.

(2) Experimental observations will be conducted with the aid of a microprocessor controlled organ perfusion system.

Significance: High concentrations of cryoprotective agents (CPAs) such as glycerol and dimethylsulfoxide are necessary for the successful cryopreservation of cells, tissues, and organs. Unfortunately, the introduction of CPAs prior to freezing and their removal after thawing has been documented in many instances to be as damaging as the freeze-thaw process itself. In order to help avoid the possible adverse osmotic effects observed by many investigators during CPA introduction and removal, a comprehensive theoretical and experimental analysis of the osmotic behavior of perfused tissue and organs is necessary.

Major Findings: Comparison of our preliminary theoretical and experimental results shows a large degree of both qualitative and quantitative agreement for the overall osmotic behavior of a perfused organ. Specifically, in both instances, a lack of high molecular solute in the perfusate seems to cause a significant gain in weight. Furthermore, our results seem to indicate that the initial weight gain during CPA removal is much greater than the initial weight loss and subsequent weight gain during CPA introduction. These similarities suggest that our work should provide some indications as to the nature of the osmotic stresses and strains which might result in tissue or organ damage during CPA introduction/removal and therefore facilitate the development of optimum CPA introduction/removal protocols.

Proposed Course: To continue our current theoretical and experimental studies of the responses of perfused organs to the introduction and removal of cryoprotective agents.

Collaborator: The experimental aspects of this project are being conducted in the laboratories of Dr. David E. Pegg, Chief of the MRC Medical Cryobiology Group, Cambridge University Department of Surgery, Cambridge, England.

Publications:

Levin, R.L.: Osmotic Effects of Introducing and Removing Cryoprotectants: Perfused Tissue and Organs". Adv. BioEngineering. (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10103-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Triple Laser - Multi Parameter Flow Cytometry System for Study of Tumor Cell Kinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
	S.E. Shackney	Acting Chief	CKS CPB DCT NCI
OTHER:	C.A. Smith	Med. Tech.	CKS CPB DCT NCI
	S.J. Occhipinti	Micro Biol.	CKS CPB DCT NCI
	H. Mujagic	Visiting Scientist	CKS CPB DCT NCI
	S.S. Chen	Visiting Fellow	CKS CPB DCT NCI

COOPERATING UNITS (if any)

DRS - NCI

LAB/BRANCH

DRS-BEIB

SECTION

ACES

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A triple laser flow cytometry system is being developed so that various imuno-fluorescent labeling techniques may be employed for the investigation of tumor cell kinetics. Three laser beams at different wave lengths will be made to intersect a tumor cell flow stream passing through a quartz cuvette so that multi-parameter signals may be obtained. These signals will be processed by specialized electronics and then analyzed by means of a PDP 11 computer.

Publications:

Shackney, S.E., Schuette, W.H., Smith, C.A., Nichols, P.W. and Lukes, R.J.: Patterns of Cell Proliferation in Relation to Aneuploidy by Flow Cytometry in the Non-Hodgkin's Lymphomas. In Proc. of 17th Annual Mtg. of the American Society of Clinical Oncology, Vol. 22, P337 April 1981

Levine, A., Shackney, S.E., Cunningham, R.E., Smith, C.A. Schuette, W.H., Teitelbaum, A.H., Nichols, P.W., Stolinsky, P.C., and Lukes, R.J.: Therapeutic Response and Survival in B and T Cell Lymphomas (LYM) in relation to tumor cell aneuploidy and proliferative state (S Fx). In Proc. of 17th Annual Mtg. of the American Society of Clinical Oncology, Vol. 22, P.520 April 1981.

Shackney, S.E., Schuette, W.H. and Lukes, R.J.:The Proliferative Behavior of Human Lymphomas. In Lymphomas Revisited: New Approaches to the Evaluation of Neoplastic Lymphoproliferative Disorders, (Lukes, R.J. and Parker, J.W., Editors) Churchill, Livingstone, New York (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10104-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Isothermia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. Talbot	Mechanical Engineer	ACES BEIB DRS
OTHER:	J. Ehrenkranz	Clinical Associate	NICHD DEB

COOPERATING UNITS (if any)

NICHD

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS/NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.4	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The secretion of thyrotropin (TSH) from the human pituitary is characterized by a 2-5 fold increase in TSH concentration in blood during the early morning, corresponding to the time of fall in body temperature. This variation in TSH occurs without corresponding changes in T_3 and T_4, the hormones which serve as the main factors in the classical feedback regulation of TSH secretion. It also appears to be not related to the onset or stage of sleep. Somatostatin infusion given in the early morning as well as pharmacologic doses of glucocortoids will decrease serum TSH concentrations in normal individuals, but it is not yet clear whether these hormones play any role in TSH regulation under physiologic circumstances.

Z01 RS 10104-01 BEI

Objective: Prevent the night-time fall in core body temperature to investigate the corresponding effect of the nocturnal TSH peak.

Methods Employed: A synthetic thermoregulatory system has been constructed. A core body thermometer is placed on the anterior chest wall. This is connected via the GPIB to the Tektronix 4052. The computer reads the core temperature and adjusts a heating suit as required to maintain a core temperature to .1^{o}C of a preset level. Appropriate safety precautions are included.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10105-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Adaptation of an EPICS II Flow Cytometer for T. Cruzi Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.E. Hall	ACES, BEIB, DRS
	J.S. Dvorak	LPD NIAID

COOPERATING UNITS (if any)

LPD-NIAID

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.8	.7	.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An EPICS II Flow Cytometer is being used to perform cytometric analysis on a unicellular protozoan known as trypanosoma cruzi, the causative agent of Chagas disease. The EPICS II is composed of a fluid flow system for hydrodynamic focusing, a laser for excitation, signal processing electronics for data acquisition and a computer for data analysis. Developmental work is being carried out upon this system in order to improve the quality of the data acquired and the way in which it is analyzed. This includes modification of the various sensing systems to increase signal to noise ratio and the interfacing of a graphic display system in order to expand the data processing capability.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10106-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Study of Fluorescein and Dextran Uptake in Tumors Using Chronic, Implanted Fiber Optic Probes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L.Levin	Mechanical Engineer	BEIB DRS
	R.L.Dedrick	Chief	ChES BEIB DRS
	P.M.Gullino	Chief	LPP NCI

COOPERATING UNITS (if any)
LPP-NCI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.5	0.8	3.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Using an in vivo micro-fluorimetry system previously developed, we have employed carboxy fluorescein and fluorescently-tagged dextran tracers in an attempt to characterize the mass transport characteristics of solid tumors.

Objectives: To monitor the mass transport characteristics of solid tumors in order to facilitate the development of optimum drug modalities.

Significance: In growing tumors, the distribution of chemotherapeutic agents varies widely as a result of angiogenesis and necrosis. A quantitative understanding of mass transport in tumors is therefore essential for the development of optimum drug modalities. Unfortunately, common assay techniques requiring the dissection of tumors tend to mask these dynamic changes by yielding spatial distributions of marker substances at only a single instance of time. To facilitate the study of the transport properties of solid tumors under dynamic conditions, two new techniques have recently been developed. These techniques permit the direct in vivo long term monitoring of the concentration time course of fluorescently-tagged substances. This study involves the use of one of these techniques, namely, the in vivo microfluorimetry method previously developed in the laboratory, to monitor the transient mass transfer characteristics of solid tumors.

Major Findings and Proposed Course: Our results indicate that the transport of low molecular weight carboxy fluorescein is not "flow-limited" and that the transport of dextrans of molecular weights ranging from 20,000 to 150,000 daltons is not "membrane-limited." We are currently in the process of developing suitable transport models which will not only adequately describe our experimental findings but will also be capable of yielding values for the perfusion rate Q and the vascular permeability coefficient K.

Publications:

Levin, R. L., et al.: "A Microfluorimetry Study of Tumor Transport Characteristics", Adv. in Bioengineering, 1981 (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10107-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Osmotic Behavior of Epithelial Cells

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L.Levin	Mechanical Engineer	BEIB DRS
OTHER:	K.R.Spring	Senior Investigator	LKEM NHLBI
	J.L.Stephenson	Senior Investigator	DIR NHLBI

COOPERATING UNITS (if any)
LKEM-DIR-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.05		

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Although water and ion transport by epithelia has been extensively studied during the last 25 years, several key pieces of information have yet to be obtained or are still in question. This includes accurate values for the passive (or possibly active) rate of water transport through epithelia, accurate values for the rate of passive and active ion transport through epithelia, and the precise manner in which epithelia regulate their size and the composition of their intracellular solution. The purpose of the present study is therefore to analyze the osmotic behavior of isolated epithelial cells.

Purposes: (1) To analytically characterize the osmotic behavior of epithelial cells. (2) To deduce from experimental observations of the osmotic responses of epithelial cells to changes in the composition of their suspending solutions, membrane(s) permeabilities of water and various ions.

Methods Employed: Mathematical modeling will be accomplished through the use of NIH's DEC-10 computing system.

Significance: The transport of water and ions across membrances is one of the basic ways in which cells maintain their normal biological activity. Study of the epithelial ion and water fluxes will therefore greatly enhance our knowledge about a fundamental life-sustaining activity.

Proposed Course: To continue the theoretical and experimental work already being conducted by Dr. K. Spring and associates of the Kidney and Electrolyte Branch of NHLBI.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10108-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Thermodynamic Behavior of Cells and Tissues at Subzero Temperatures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L.Levin	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.06		

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

During the past twenty years, numerous models have been proposed to describe the osmotic behavior of biological cells during freezing and thawing. Although these studies have pinpointed the important biophysical parameters governing the volumetric response of cells at subzero temperatures they all have one serious drawback. Namely, all of the current models deal with a single, isolated cell suspended in an infinite amount of bathing solution which is being cooled or warmed uniformly at a constant rate. No provision is made for those common situations where (1) the volume of cells is comparable to the volume of the suspending solution or (2) the cellular system is cooled or warmed in a non-uniform manner with time due to the inability of the freeze-thaw device to handle the large amount of latent heat generated during freezing or adsorbed during thawing. The purpose of the present study is therefore to analytically investigate cellular osmotic behavior under non-ideal, but typical, freeze-thaw conditions.

Objectives: To analytically characterize the behavior of biomaterials during freezing and thawing in order to facilitate progress in attempts to successfully freeze-preserve cells, tissues and organs.

Methods Employed: Mathematical modeling will be accomplished through the use of NIH's DEC-10 computing system and associated computer graphics facilities.

Significance: Cryopreserving biological materials such as blood, sperm and ova, skin, and various other types of cells and tissues in research institutions and hospitals is a matter of great practical convenience since extremely low temperatures curtail metabolism and degenerative biochemical reactions. In fact, most biomaterials could probably be stored for milenia in a cryogenic environment. Unfortunately, in order to achieve this goal, cellular survival must be ensured during the critical cooling and warming periods associated with this form of storage. Consequently, further progress in the successful cryopreservation of cells, tissues, and organs necessitates an increased understanding of both the physical chemical events and the cellular responses that occur during a freeze-thaw cycle.

Major Findings: Our results indicate that the cytocrit of the cell suspension (Volume Cells/Total Volume Suspension) begins to significantly affect cellular volumetric behavior at levels above 10%. This is especially true for pre-frozen cell suspensions which are being warmed at very high rates in which case the cells are exposed to strongly hypotonic conditions just after the complete melting of the extracellular ice. Our results also indicate that most of the cellular water loss during freezing or gain during thawing may occur during the long temperature-time plateaus which usually occur just after the initial formation of extracellular ice during cooling and just before the final melting of the extracellular ice during warming rather than at lower or high temperatures.

Publications:

Levin, R.L.: "The Heterogeneous Freezing and Thawing of Aqueous Solutions." Trans. ASME. (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10109-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Adjunct Heat Treatment of Cervical Cancer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L.Levin	Mechanical Engineer	BEIB DRS
	E.J.Glatstein	Chief	ROB NCI

COOPERATING UNITS (if any)
ROB-NCI.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.02		

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to facilitate the development of adjunct hyperthermia treatments of cervical cancer by theoretically and experimentally studying the spatial and temporal variation in the temperature field of tissues subjected to microwave EM radiation.

Objectives: (1) To develop a generalized mathematical model which will predict the spatial and temporal variation of the temperature field within a tissue of organ subjected to microwave irradiation. (2) To measure the spatial and temporal variation of the temperature field in the cervical area of humans undergoing therapy. (3) To facilitate the development of optimal adjunct hyperthermia modalities.

Methods Employed: The mathematical modeling will be accomplished through the use of NIH's DEC-10 computing system and associated computer graphics facility. The experimental measurement of the temperature field within tissues subjected to microwave radiation will be accomplished through the use of a newly available electromagnetically insensitive fiber optic temperature probe.

Significance: At present the heat treatment of carcinogenic cells when combined with conventional radiotherapy and chemotherapy shows considerable promise in the management of cancer. Nevertheless, there still remain numerous important problems that must be resolved. Of paramount importance is the problem of generating and controlling uniform temperature fields within tissues. This study will therefore attempt to facilitate the development of optimum hyperthermia modalities by theroretically and experimentally studying the temperature fields within tissues subjected microwave EM radiation.

Proposed Course: To begin the development of a suitable mathematical model utilizing the "bioheat" transfer equation. To interface the temperature measurement study with the clinical trials of the Radiation Oncology Branch of NCI.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10110-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Design of a Dual-3 Dimensional Position Monitor for Speech Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.C. Walker	Mechanical Engineer	BEIB, DRS
OTHER:	C.L. Ludlow	Lab of Comm. Disorders	NINCDS
	M. Dorn-Quine		

COOPERATING UNITS (if any)

NINCDS

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.25	.25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An instrument to monitor facial movements during articulation has been designed. The device consists of two, mirror image, transducers mounted on a common head frame. Each transducer, which can be individually adjusted, is capable of measuring the movement of a point in three orthogonal planes. The primary use of this instrument will be to study the lip movement of both normal and abnormal subjects.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10111-01

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Analytical High Voltage Electron Microscopy and Mirage Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.C. Gibson	Electronics Engineer	BEIB, DRS
OTHER:	R.D. Leapman	Physicist	BEIB, DRS
	C.E. Fiori	Physical Scientist	BEIB, DRS
	K.E. Gorlen	Electronics Engineer	CSL, DCRT
	L.K. Barden		CSL, DCRT
	J.S. Delpriore		CSL, DCRT
	C.R. Swyt	Physicist	BEIB, DRS

COOPERATING UNITS (if any)

Computer Systems Laboratory, DCRT

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.5	4.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The computer interface for the 200 KeV Hitachi 7000 Electron Microscope is approximately 80% complete. When complete, the computer will be able to control the microscope to acquire bright field images, dark field images, x-ray images, and electron energy loss images, simultaneously as well as directly, being able to measure the beam current. The computer-microscope combination will also be able to acquire energy dispersive x-ray spectra and electron energy loss spectra. Energy selective elemental imaging will also be done.

Objectives: To provide a computer controlled 200 KeV analytical electron microscope suitable for studying biological samples using energy dispersive x-rays and electron energy loss.

Methods Employed: Major modifications have been made to the microscope to enable it to be controlled by the computer. We have also redesigned the spectrometer electronics to provide 60Hz AC field connection, faster pulse counting circuitry, an alignment circuit, and a remote magnet control.

Significance: The computer controlled acquisition system will allow the data to be collected more rapidly, therefore minimizing the radiation damage to the specimen. The other modifications have improved the resolution for energy loss by a factor of five and the count rates by 10^4.

Proposed Course: Complete the interface circuiting and add 120Hz AC field connection, Descanning circuits for the beam, and a Faraday cup to measure beam current.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10112-01

PERIOD COVERED

October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Analysis of Microcirculation by Coherent Light Scattering

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Bowman	Chief, Lab. Tech. Dev.	LTD NHLBI
	P.D. Bowen	Biologist	LTD NHLBI
	R. Bonner	Physicist	BEI DRS
OTHER:	R. Nossal	Physicist	PSL DCRT
	A. Tahmoush	Clinical Associate	NB NINCDS

COOPERATING UNITS (if any)

Biomedical Engineering and Instrumentation Branch, DRS

LAB/BRANCH

Laboratory of Technical Development

SECTION

NHLBI

INSTITUTE AND LOCATION

NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is the development of a clinical, non-invasive monitor of tissue blood flow by analysis of the spectrum of Doppler scattered laser light. The NIH Laser Doppler Blood Flow Monitor has been demonstrated to be highly portable and clinically convenient with the new flexible 4m fiber optic probes and photodiode detection system. The probes withstand sterilization procedures and mechanical insult well and are suitable for operating room patient study. The linearity of the flow analysis processor has been demonstrated in a variety of tissues and clearly resolves physiologic flow changes including instantaneous pulsatile flow in the microcirculation. Muscle blood flow in over 50 patients with neuromuscular disease has been studied and preliminary data suggest that post occlusive reactive hyperemia responses may be primary or secondary indicators of disease state. Studies of scleroderma patients' skin blood flow have shown markedly reduced flows in advanced scleroderma with very high flows at telangiectasia. Clinical applications being developed for the instrument are: allergy testing - quantitative methodology, periocular blood flow as indicator of external-internal carotid artery flow and implied flow to circle of Willis.

Objectives: Ongoing clinical applications include muscle blood flow at open muscle biopsy in muscular dystrophy patients, skin blood flow in normals and scleroderma patients and potential for therapy assessment, skin blood flow in periocular and facial regions of patients with carotid artery occlusive disease as potential alternative to angiography, and allergy testing using quantitative skin flow responses. Specific objective at this stage is the application of the instrument and technique in the above variety of clinical and experimental problems.

Methods Employed: The present form of the apparatus has demonstrated its clinical convenience and portability.

Major Findings: (1) The fiber optic probe system greatly improved the convenience of remote and flexible attachment to the patient; (2) The mean frequency detection used to analyze the Doppler shifted light signal has proved to be the optimum analysis method for diffuse tissue scattering. We developed a rigorous theory which substantiates the validity of our analysis method. Empirically output flow levels in a given tissue as well as between tissues correlate well with alternative measures of flow cited in literature. Our output corresponds to 1 volt = 15 ml/min/100g tissue. Interacting with other researchers we have demonstrated the correctness of our processor algorithm and are actively communicating with commercial developers to insure that the proper analysis scheme is employed in the commercial version of this instrument; (3) Studies of human tissue blood flow have been conducted under several protocols at the Clinical Center and other locations. In addition to measurements of skin blood in clinical center patients and normals, we have made extensive measurements of human muscle blood flow in over 50 patients during open muscle biopsy. Resting flows and post occlusive reactive hyperemia were monitored. Preliminary data analysis suggest that there are flow levels and responses which may be primary or secondary indicators of the various muscle "organ" disease state. We have made measurements of clinical center patients and normals in the periorbital region of facial skin and have found differences in flow and response to carotid occlusion for the patients not found in normals. Our experiments indicated abnormal zygomaticorbital skin flow in one patient whose retinal arteries were becoming occluded with clots. Our goal was to be able to infer external carotid and internal carotid artery blood flow and implied flow to the circle of Willis and brain. Studies of blood flow and local contractility of epicardium and endocardium of the dog heart have shown that the complex wave form obtained in beating heart muscle can be analyzed as to separate contractile and flow curves by averaging over several cardiac cycles and subtracting a no-flow, contraction only signal from the combined signal.

Proposed Course: (1) Continue development of the instrument in collaboration with LTD and industry; (2) Cooperate in clinical trials to establish the instrument as a useful clinical and experimental tool.

Significance: The NIH Laser Doppler Blood Flow Monitor is an instrument which holds promise for study of the local tissue microcirculation. It has potential applications in the research laboratory, and in the clinical study of vascular disease, peripheral vascular disease, allergy-skin flow testing, screening of vaso-active drugs, and the monitoring of patients with unstable circulatory systems.

ublications:

Bonner, R.F.,Bowen, P.D., Clem, T.R., Nossal, R.: Laser Doppler Continuous Real Time Monitor of Pulsatile and Mean Blood Flow in Tissue Microcirculation Scattering Techniques Applied to Supramolecular Non-equilibrium Systems, Plenum press, 1981, p. 279-316.

Bonner, R.F. , Nossal, R.: A Model for Laser Doppler Measurements of Blood Flow in Tissue, Applied Optics, 20: 2097-2108, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10113-01 BEI

PERIOD COVERED
October 1, 1980 to September 30, 1981.

TITLE OF PROJECT (80 characters or less)

Nuclear Magnetic Resonance Imaging System for Infants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. I. Hoult	Visiting Scientist	BEIB DRS
OTHER:	C.-N. Chen	Visiting Fellow	BEIB DRS
	F. Romeo	Guest Worker	BEIB DRS
	M. S. Silver	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)

NICHD

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Nuclear Magnetic Resonance Imaging

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	4.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

One interesting and potentially extremely valuable application of NMR in medical diagnosis is the generation of two- or three-dimensional images within living subjects. Clear images of the distribution of water in biological objects, including humans, have been obtained with image reconstructions methods.

The system being developed within BEIB utilizes a novel spherical electromagnet completed as part of an earlier project and described in an earlier report. The NMR signals will be produced and processed by a novel pulse Fourier transform method, rotating frame zeugmatography. The major goal of our approach is to produce images of high quality in time intervals that are a fraction of the time required by other methods.

Objectives: The purpose of this project is to develop an NMR resonance imaging or zeugmatography system to be used for exploring applications of NMR to medical imaging. The size of the device will permit examination of babies with the primary goal of detecting fluid filled lesions.

Methods Employed:

Field Homogeneity

The magnetic field is being analyzed in spherical harmonics. The effects of dipoles and metal strips and rings on various orders of the field are being computed and verified experimentally. Homogeneity of 3 - 5 ppm can now be obtained in a volume of 18cm in diameter.

Contrast Optimization

The theoretical approach calls for establishing an optimum pulse sequence by maximizing the change in signal-to-noise ratio with respect to change in relaxation time so that a good contrast in relaxation times can be obtained in the image.

Flux Stabilizer was built to stabilize the magnetic field. Short time stability is better than we can measure - about 1 part in 10^7.

Array Processor

An Analogic Array Processor has been installed. Hardware and software are being modified to perform part of the calculations during the time of data collection. Collection of the data (1024 complex values), base line correction, followed by FT and display are now being performed in 25 msec.

Display System

A software package has been installed in large measure. The standard software is being modified in order to comply with the upgraded display hardware.

Computing

The core memory of the PDP 11/34 is being expanded to 256 KB. An extended memory monitory has been generated. A virtual memory device handler will be installed. All tests dealing with the method of computation have been done and the RT11 operating system has been patched where it was found to be deficient.

RF Probe

A large RF probe made from copper tubing has been constructed. It is tuned to 5MHz, the Q factor of the transmitting coils being about 600, while that of the receiver is about 900. The transmitting coils are capable of producing the requisite RF field with gradients established in the laboratory frame.

Proposed Course: The pulse programmer will be constructed. The display system will be expanded so as to accept 12 bits of digitized data. The entire system will be integrated with the PDP 11/34. Experiments in producing two dimensional images will be carried out on suitable phantoms.

Annual Fiscal National

LIBRARY
NIH
Amazing Research.
Amazing Help.
http://nihlibrary.nih.gov

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

NIH LIBRARY
3 1496 00178 5057